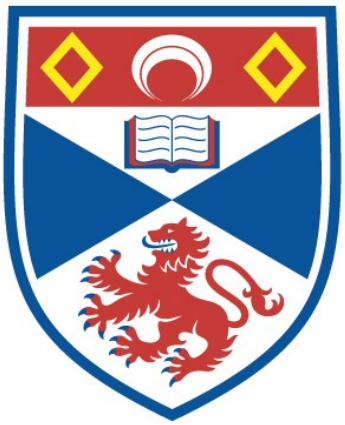
NOVEL DERIVATIVES OF DPP AND RELATED HETEROCYCLES

Colin J. H. Morton

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1999

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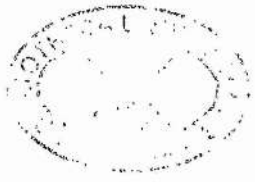

Declaration

I, Colin J.H. Morton, hereby certify that this thesis has been composed by me, that it is an accurate representation of the work undertaken by me in the University of St. Andrews since my admission as a Research Student on 1 October 1996, and that it has not been accepted in any previous application for any Higher Degree or professional qualification.

September 1999 Signed...

I hereby certify that Colin J.H. Morton has fulfilled the Regulations appropriate to the Degree.

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I offer my sincere thanks to Dr. David Smith for his guidance during the past three years of research, for his constructive criticism when required and for reaffirming my enjoyment of chemistry.

I extend my thanks to Ciba Speciality Chemicals (Basel, Switzerland) for funding this work. In particular, I am grateful for the inspiration and creative input of Prof. Abul Iqbal, and for the pragmatic, forthright contribution of Prof. Ian Macpherson since his retirement.

This thesis would be much shorter without the excellent portfolio of X-ray structural analysis provided by Dr. P. Lightfoot, Dr. E.J. Maclean (Daresbury Laboratory), Prof. G. Ferguson (University of Guelph, Canada) and Dr. A. Slawin. To each of these chemists I am indebted

I thank Dr. C. Glidewell, Dr. D. Lloyd, Dr. A. Aitken and Dr. M -J. Tremayne for helpful discussions and Mrs M Smith, Mr C. Millar and Mrs S. Williamson for NMR, mass spectral and elemental analyses respectively.

To my fellow students, former members of the group and the wider staff of the School of Chemistry, I offer my thanks for providing a healthy atmosphere in which to pursue my studies.

Lastly, I am very grateful for the support of my parents and family, without which none of this would have been possible.

"Science is nothing but trained and organised common sense, differing from the latter only as a veteran may differ from a raw recruit: and its method differ from those of common sense only as far as the guardsman's cut and thrust differ from the manner in which a savage wields his club"

Thomas Henry Huxley (1825-1895)

Abstract

This thesis discusses the synthesis of new organic, heterocyclic materials for potential application as pigments.

Chapter 1 comprises an introduction to the field of pigment and dye chemistry, discussing the rudimentary elements of colour theory, before advancing to a review of the pertinent literature regarding high performance organic pigments. In particular, the development of 1,4-diketopyrrolo[3,4-*c*]pyrrole (DPP) pigments is described and the central objective of synthesising alkenyl-DPPs is outlined.

Chapters 2 and 3 describe synthetic efforts towards alkenyl-DPPs, employing retro Diels-Alder methodology. The reactions involving the furan-acrylonitrile adduct as the nitrile component in the standard DPP synthesis led mainly to aromatisation of the bicyclic system and the cyclopentadiene-acrylonitrile adduct failed to react altogether. The explanation for this failure has been investigated. In the course of this these studies, several DPPs incorporating a secondary alkyl substituent were prepared, not least a novel cyclohexenyl-DPP.

Chapter 4 describes the use of α,β-unsaturated nitriles in the standard DPP synthesis. These behaved as Michael acceptors and in the case of cinnamonitriles led to a new family of coloured materials, namely substituted 4-hydroxy-2*H*-cyclopenta[*c*]pyrrol-1-one-5-carbonitriles.

Chapter 5 describes the corresponding reaction of cinnamate esters, but in these cases bicyclic systems were not formed. The reactions are analogous to Claisen acylations and the stereochemistry of the products varied according to the substituents.

Chapter 6 contains the detailed experimental work for these investigations and concludes with a portfolio of X-ray structural data.

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Chapter 1

INTRODUCTION

Chapter 2

THE PREPARATION OF ALKENYL-DPP MONOMERS

Chapter 3

ALTERNATIVE APPROACHES TO ALKENYL-DPP PRECURSORS

Chapter 4

THE SYNTHESIS OF DPP ANALOGUES

Chapter 5

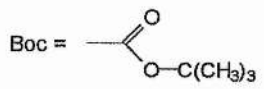
CINNAMATE ESTERS IN THE STANDARD DPP SYNTHESIS

Chapter 6

EXPERIMENTAL

Acronyms and Abbreviations Used

Reagents and Solvents

Boc_2O	di-(*t*-butyl) dicarbonate
Boc =	
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPP	1,4-diketopyrrolo[3,4-*c*]pyrrole
TFA	trifluoroacetic acid
TMS	tetramethylsilane

Miscellaneous

COSY	correlation spectroscopy
DSC	differential scanning calorimetry
ROMP	ring opening metathesis polymerisation

All colour diagrams provided for the structures resulting from X-ray analysis were produced using a 'Diamond 2.0' software package for PC

Chapter 1

INTRODUCTION

1.1 PIGMENTS AND DYES

1.1.1. Definition

A pigment is any finely divided insoluble white or coloured solid material, which is primarily used to improve the appearance of or give colour to the medium in which it is applied. Pigments and dyes are often derived from similar chemical building blocks, but the essential technical distinction between the two is that a dye is soluble in its application medium whereas a pigment is not. Dye molecules form an attachment to the molecules they colour - either a physical link (e.g. hydrogen bond) or a chemical bond, whereas pigments cover up the base material underneath by providing a coating of aggregate particles or microcrystals without dissolution of the molecules. Dyes impart colour solely by absorption of visible light whereas pigments do so by selective absorption and/or scattering of light. Pigments may be either organic or inorganic.

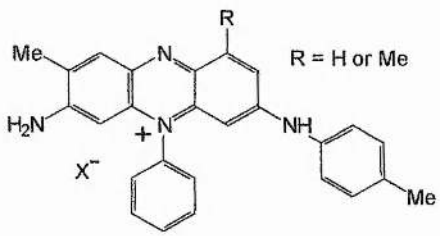
1.1.2 Properties of pigments

A pigment must demonstrate good colouristic performance; notably high light fastness, weather fastness, heat stability, chemical resistance, hiding power (opacity/transparency), solvent resistance, gloss properties and colour strength. The commercial success of a pigment depends on this. Fundamental to the usage of all commercial pigments is that the products have to be incorporated uniformly into the medium for which they are intended. Therefore, it must be possible to prepare easily a stable dispersion of the pigment, which displays desirable rheological properties. Obtaining a high quality dispersion depends upon the crystalline/particulate nature of the pigment whilst the particle size of the microcrystals in such dispersions has a direct effect on a pigment's colouristic properties.

1.1.3 History

Pigment application dates back to antiquity; natural organic and inorganic colourants have been used by man since prehistoric times. For solubility reasons, most of the organic compounds used originally would now be classed as dyes rather than pigments. The discovery of mauveine[1] (figure 1) by W.H. Perkin in 1856 followed by the discovery of the diazotisation reaction of aromatic amines by Peter Griess soon thereafter triggered the development of synthetic organic colourants.

Figure 1: Mauvine (a mixture of two components)



Much of the chemical industry of today developed primarily from synthetic dyestuff chemistry during the nineteenth century. During recent decades, organic colourants have undergone rapid growth to become an industry of considerable commercial importance and potential.

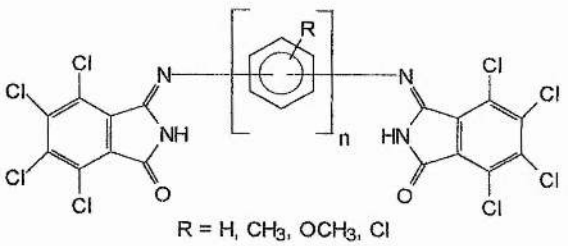
1.1.4 Classification of organic pigments

Organic pigments are diverse in both their chemical structure and their technical performance. Approximately half of the world market volume of synthetic organic pigments is comprised of compounds based upon the azo chromophore, while a quarter is claimed by metal phthalocyanines. The remaining quarter is shared by a variety of heterocyclic pigments, a few quinoid and indigoid structures and multi-dentate metal complexes[2] (figure 2).

A detailed examination of pigments by chemical structure is not conducive herein: for an extensive review of organic pigments classified by structure the reader is referred to the recent literature[3-7]. Instead, a classification based upon performance criteria will suffice and so organic pigments can be divided into *classical* and *high performance* pigments. The most common classical pigments are the azo

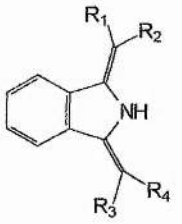
compounds, with different structures providing a range of yellow, orange and red colourings. Originally, the azo chromophore formed the basis of many organic dyes and only in later years were pigments prepared based upon this sub-structure.

Figure 2: Common classical pigment structures



R = H, CH_3, OCH_3, Cl

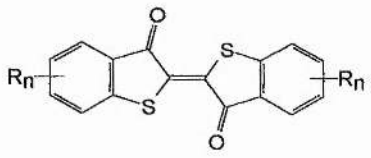
tetrachloroisoindolinone pigments



R_1-R_4 = CN, CONH-alkyl or CONH-aryl

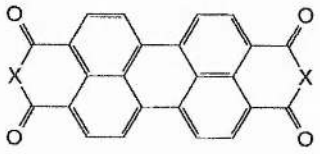
or R_1 and R_2 can be part of a heterocyclic ring system

Methine pigments



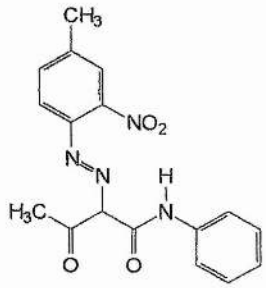
n = 2 or 3

Thioindigo pigments

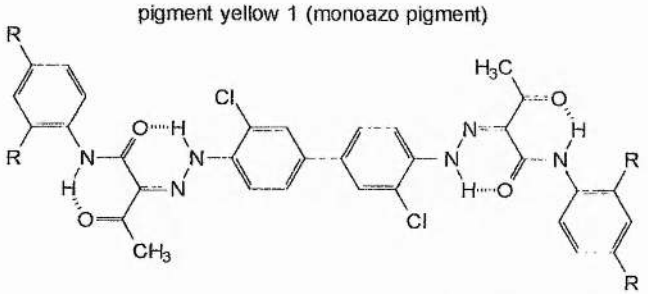


X = O, N-R

Perylene pigments

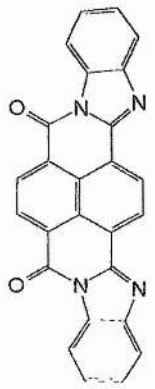


pigment yellow 1 (monoazo pigment)



C.I. Pigment Yellow 13 (R = CH_3) and C.I. Pigment Yellow 12 (R = H)

Azo pigments(monoazo and bisazo examples are shown)

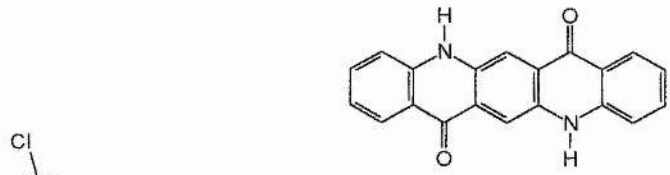


Perinone pigments

In essence there have been three major advances this century in the development of new chromophoric systems used first in a pigment application. Firstly, the copper

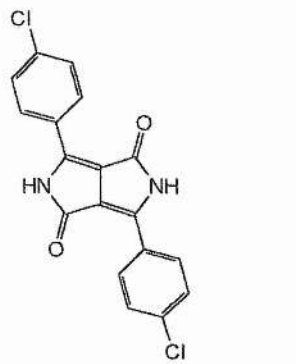
phthalocyanine pigments[8-12] of the 1930s constitute the primary group of classical blue pigments (figure 3) and only in subsequent years were soluble derivatives developed for use as dyes. Secondly, quinacridone materials (figure 3) were developed for pigment application in the 1950s by DuPont[13], providing a range of yellow to red colourings. Lastly, pigments based upon the heterocycle 1,4-**dike**to**py**rrolo-[3,4-*c*]**py**rrole (DPP) (figure 3) were developed in the 1980s by Ciba-Geigy[14]. This third class of pigments constitutes an important new class of high performance pigments, offering mainly red colourings. Until their advent, inorganic pigments such as cadmium red (C.I. Pigment Red 108) or moly orange (C.I. Pigment Red 104) were used to provide suitable solid red shades, but in many countries manufacturers have moved away from inorganic products, due to environmental issues and increasing pressure from legislation limiting the use of heavy metals. Until the 1980s, the best lead-free formulations comprised mixtures of azo, perylene and quinacridone pigments, all of which fell short of providing suitable pigment performance, particularly in automotive coatings where the technical specifications of durability are very demanding. The DPP pigments were excellent organic alternatives, offering even better pigment performance without the environmental impact[15-16].

Figure 3



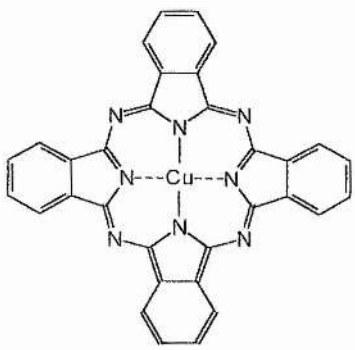
C.I. Pigment Violet 19

Quinacridone pigments



C.I. Pigment Red 254

Diketopyrrolopyrrole (DPP) pigments



C.I. Pigment Blue 15

Phthalocyanine pigments

1.2 COLOUR THEORY

1.2.1 Colour properties of pigments and dyes

Colour may result in nature from purely physical effects: a combination of reflection, refraction or interference of light in thin layers. Examples include the feathers of birds, the wings of butterflies and the colour on soap bubbles. Such colour phenomena are sometimes called structural colours. The observed colour (or hue) of pigments and dyes, however is due to the partial absorption of incident light, which causes the excitation of electrons within their molecules to higher energy levels, thereby giving the molecule the shade of the resulting complementary colour. This energy increase obeys the Planck equation (1). The excited electrons lose their excess energy via molecular collisions, emission of radiation or photochemical reaction.

$$E = h\nu = hc/\lambda \qquad (1)$$

E = energy, h = Planck's constant, c = speed of light, λ = wavelength

It is important to note that qualitative inspection of electronic spectra does not always provide the correct colour of a coloured solution or solid because the sensitivity of the human eye for different parts of the visible spectrum varies. Not only are the wavelength and intensity of the absorption maximum important, but also the shape of the absorption band. The smaller the width and steeper the slopes of the band, the purer and more brilliant the hue appears to the human eye.

It is difficult to excite σ-electrons, but excitation of the lone pairs of electrons on heteroatoms (e.g. N, O, Cl) of saturated organic compounds requires less energy and the π-electrons of isolated double or triple bonds are even more easily excited. When conjugation becomes possible between two or more pairs of π-electrons, the energy gap between the π and π^* orbitals decreases and strong absorption becomes possible in the near UV or visible region corresponding to π-π^* transitions. Hence, the pattern or system of conjugated double bonds primarily defines the colour of an organic molecule.

Classically, the ideas of colour can be explained via chemical means. Pigment and dye molecules contain a *chromophore* (an unsaturated group such as an aromatic,

carbonyl, azo, azomethine, ethylene, or nitro) and an *auxochrome* (a substituent on the chromophore such as a hydroxy, amino, methoxy and dimethylamino group). It has become apparent that auxochromes are electron donors and that chromophores are electron acceptors (linear or cyclic systems of conjugated double bonds). Auxochromes and chromophores are now best regarded as p- and π-electron bearing-groups respectively. These groups lead to a delocalised electron distribution within the molecule, and hence absorption of incident visible light. An accumulation of chromophores within the molecular structure, particularly when these are conjugated, brings about a shift to longer absorption wavelength, and thus to a different observed colour.

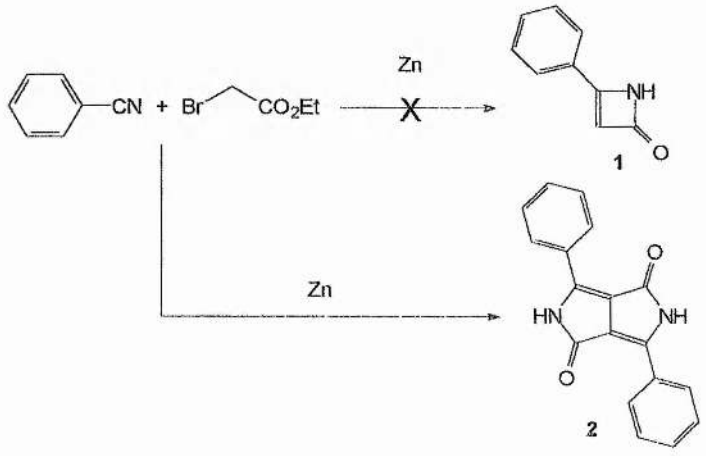
To augment these classical ideas of colour, quantum mechanics can now be used to interpret and/or predict the light absorption characteristics (i.e. the electronic spectra). In principle, the absorption frequency of a molecule can be calculated if the energies of the ground and excited states are known. Solution of the Schrödinger wave equation in complex molecular assemblies of atoms, as encountered in pigments or dyes, rapidly becomes mathematically difficult, and methods of approximation, such as the *molecular orbital method*, become necessary. Electronic spectra of such compounds are primarily explained by π-electron transitions, and in particular $\pi \rightarrow \pi^*$ transitions dominate. Finally, it should be noted that fluorescent organic compounds are characterised by stiffness in their structure, which prevents the energy of the excited state from being lost through torsional vibrations of the molecule. In the case of DPP such a structural observation is apparent, and indeed fluorescence is observed in many derivatives.

1.3 HISTORY & DEVELOPMENT OF DPP PIGMENTS

1.3.1 Introduction and original synthesis

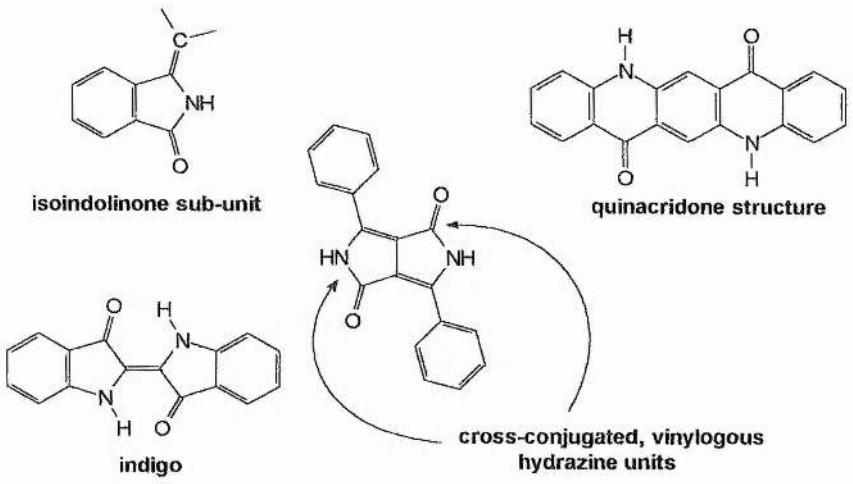
In 1974, Farnum *et al.*[17] were interested in the synthesis of derivatives of the 2-azetinone **1** which they attempted via a modification of the Reformatsky reaction, starting from benzonitrile and ethyl bromoacetate (figure 4). The target molecule was not obtained. Instead, a brilliant red compound was isolated in 5-20% yield, and characterised as the 3,6-diphenyl-DPP derivative **2**. Several other by-products were obtained from the reaction.

Figure 4: Original discovery of diphenyl-DPP



In 1980, chemists at Ciba-Geigy discovered this work whilst scrutinising the published literature and were immediately interested by the product's structure which comprises indigo-like, cross-conjugated vinylogous amidic chromophore units embedded in a rigid, planar structural frame.[18-21] This structure bears a strong resemblance to the isoindolinone structure below, and the concealed vinylogous hydrazine and α-diketone sub-structures within DPP could be compared to the structural elements within the classical quinacridone pigment (figure 5). This structural resemblance coupled to the high melting point of the product and its high insolubility prompted an investigation of its performance as a pigment. Preliminary testing showed highly promising pigment fastness properties. Immediately, other novel DPP derivatives were prepared via the Reformatsky route and suitable initial patent protection sought.[22]

Figure 5: Structural comparison of DPP with existing pigments

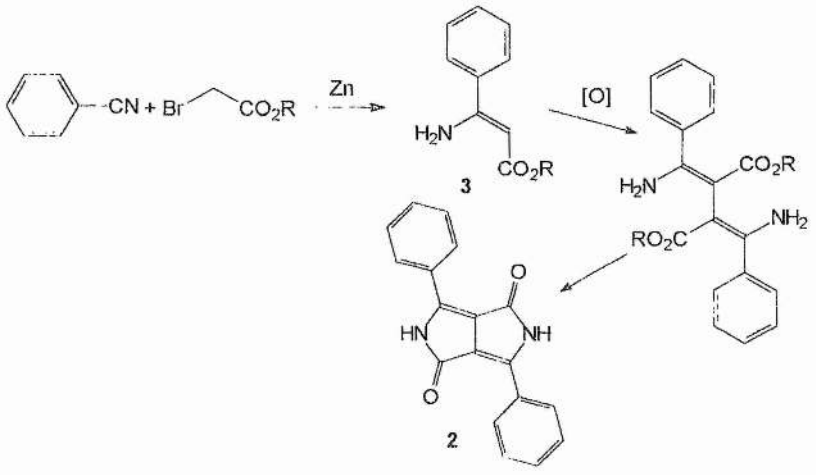


Efforts were then targeted at examining the mechanism for formation of this product with the intention of optimising the reaction for commercial production.

1.3.2 Mechanism of DPP formation via a modified Reformatsky reaction

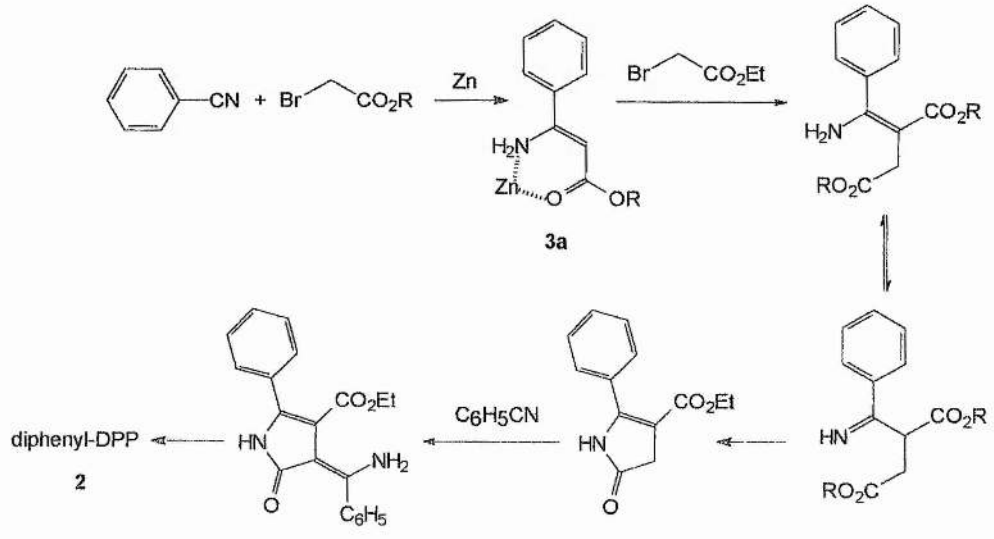
Farnum *et al.* proposed that formation of the DPP derivative occurs mechanistically via oxidative dimerisation of the expected Reformatsky product **3** from benzonitrile and ethyl bromoacetate, with or without participation of the metal centre (figure 6).

Figure 6



Subsequently, the group at Ciba-Geigy provided evidence supporting the intermediacy of the enamino-ester **3** and its zinc salt **3a**. However, oxidative coupling of this independently synthesised intermediate could not be achieved, negating Farnum's earlier hypothesis. Instead, a unified mechanistic rationale (figure 7) was proposed, based upon the observation that the independently prepared zinc salt of the intermediate **3**, when added to a mixture of benzonitrile and ethyl bromoacetate only, furnished the DPP derivative **2**. Optimum yields based on this new proposed mechanism were only 25-30% (calculated on bromoacetate), still too poor to warrant commercial production. Nonetheless, this technology was covered by suitable patent protection.[23-24]

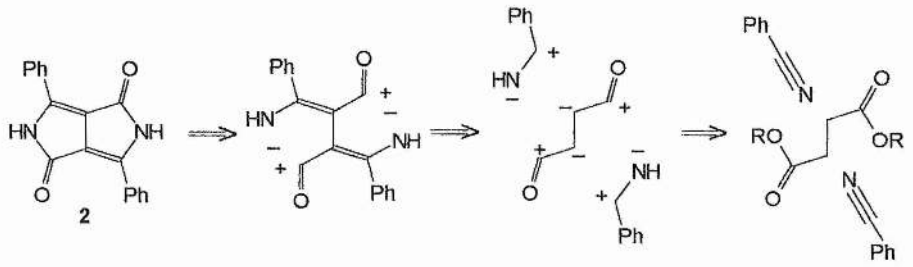
Figure 7



1.3.3 Development of commercial DPP synthesis

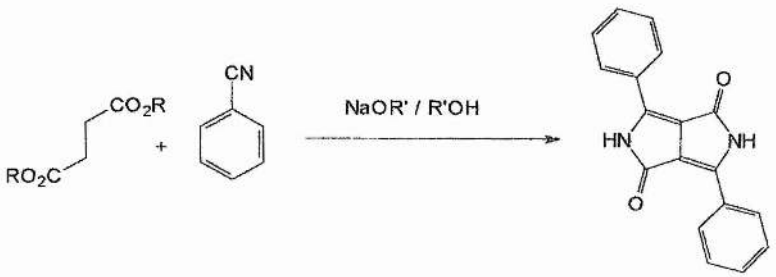
Inspection of the Reformatsky reaction mechanism showed that the low yields of the DPP final product were in sharp contrast to the observed high yields of the zinc salt **3a**, from which it was concluded that the yield-determining step was the *C*-alkylation of the zinc salt. A new synthesis was developed in which the yield-limiting *C*-alkylation step was overcome via incorporation of the necessary bond into the starting reagent. The relevant disconnections are shown in figure 8.

Figure 8



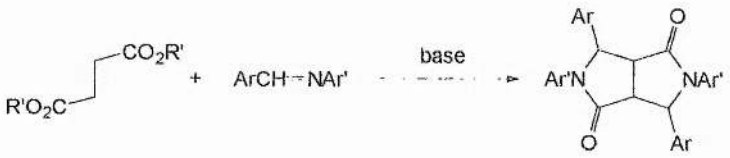
The synthesis, starting from succinic esters and aromatic nitriles, was attractive because it afforded the desired product **2** in a one-step process from readily available starting materials, with the central C-C bond already incorporated into the succinic ester (figure 9).

Figure 9



This reaction resembles the classical Stobbe condensation reaction, which entails the reaction of a succinic ester with an aldehyde or its Schiff base[25] (figure 10).

Figure 10



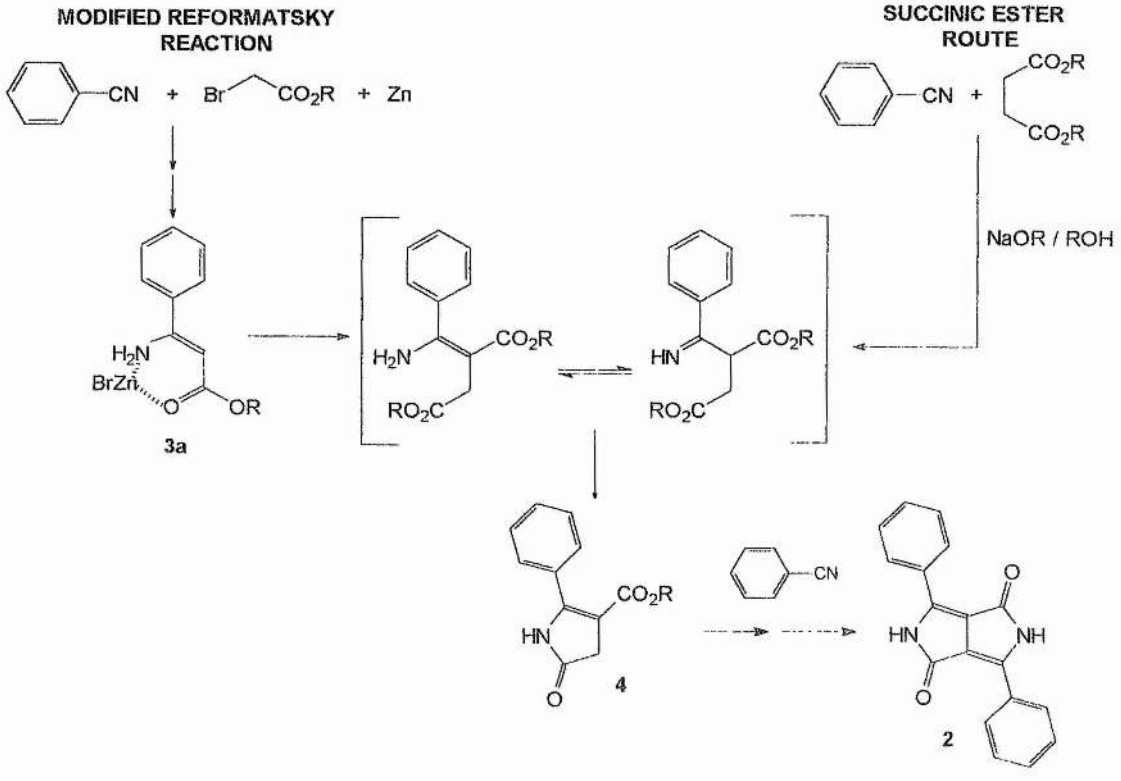
The relatively low electrophilicity of the nitrile and base-catalysed Claisen reaction of the succinic ester were important side reactions to be considered. For successful DPP synthesis by this route, a sufficiently strong alkoxide base of poor nucleophilic reactivity was required, thus ensuring deprotonation of the succinic ester along with minimum loss of reactants via nucleophilic attack at the nitrile or at the ester

carbonyl group. Slow addition of the succinic ester during the reaction ensured a low steady-state concentration to help suppress self-condensation. To this end, optimum yields were obtained with branched alcohols employed both in the base and succinic ester derivative. The synthesis was optimised for commercial production.[26-28]

1.3.4 Review of current DPP synthetic methods

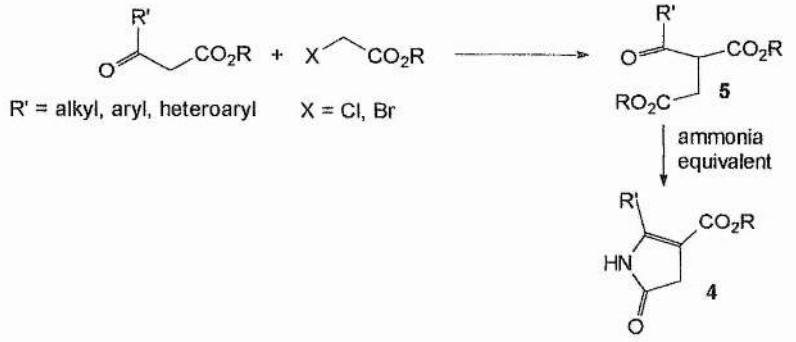
The synthesis of diphenyl-DPP **2** starting from benzonitrile and a succinic ester was understood to proceed via the pathway shown (figure 11) on the basis of the evidence discussed earlier.

Figure 11



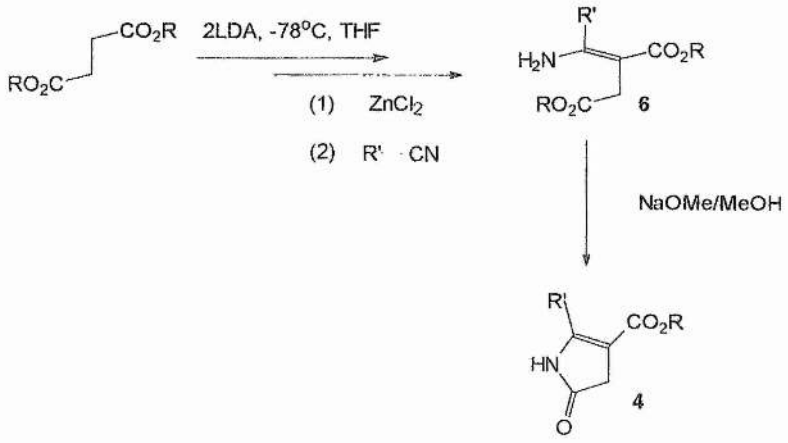
The pyrrolinone ester intermediate **4** postulated for the original Reformatsky route could be isolated and characterised independently by cyclising a compound of formula **5** with an ammonia equivalent, e.g. ammonium salts (figure 12).

Figure 12



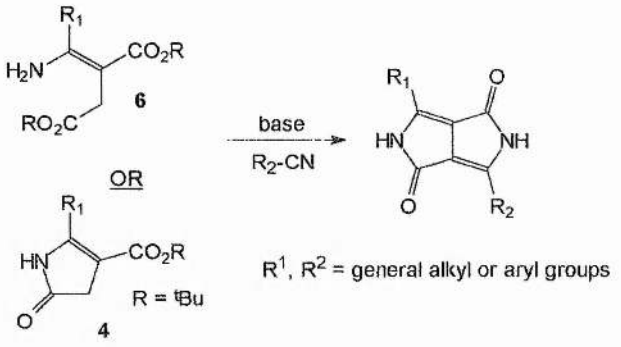
Furthermore, the ester **4** can be prepared direct from a dialkyl succinate and a suitable nitrile via use of lithium diisopropylamide base (figure 13). In this case, exchange of the metal ion with zinc chloride is critical in ensuring that reaction occurs, due to the incapability of the lithium ion to take the nitrile group into its ligand sphere.[29]

Figure 13



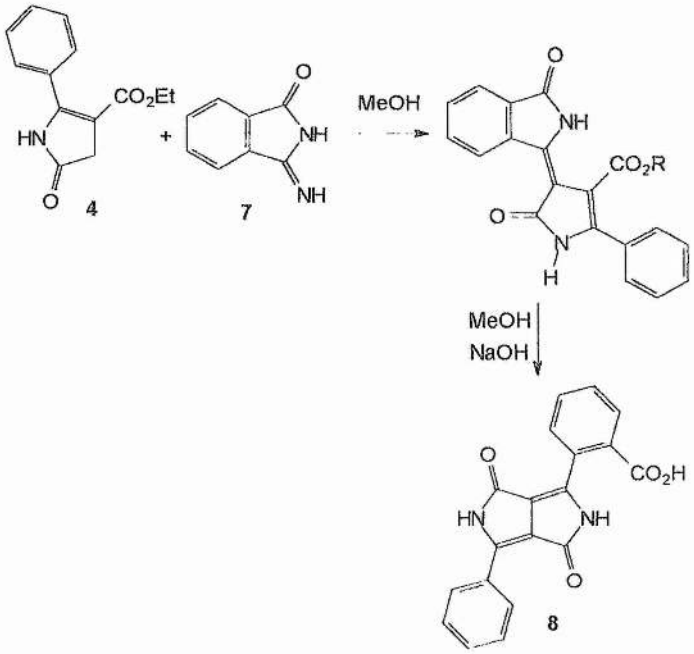
The intermediate pyrrolinone ester **4** or its non-cyclised enamino ester precursor **6** could be employed in reaction with a suitable nitrile (analogous to the standard commercial synthesis in figure 9 above) to give the desired DPP products in excellent yield, providing a facile route to unsymmetrically substituted alkyl- and aryl- DPP derivatives (figure 14). These developments are described in detail within a number of patents.[30-31]

Figure 14



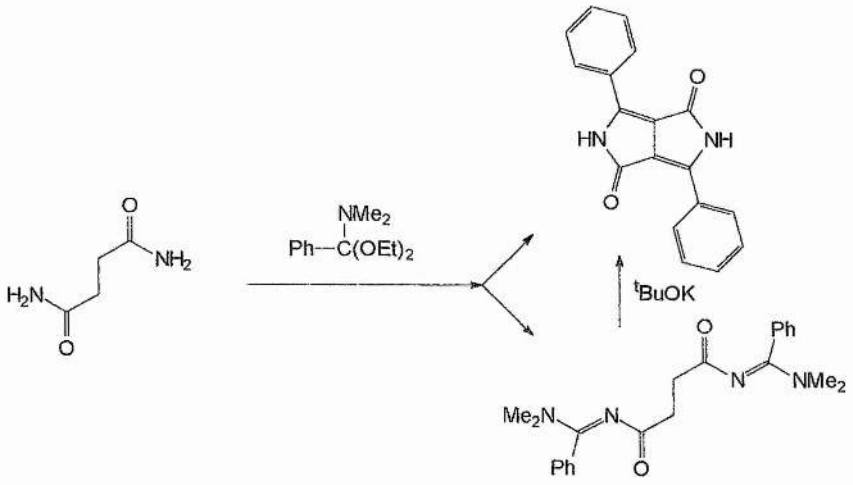
The pyrrolinone ester **4** was found to react with a variety of electrophiles due to its acidic active methylene grouping. An example of particular relevance is the reaction with imino-isoindolinone **7** which upon ring closure with sodium hydroxide ultimately gives the *o*-carboxy-substituted DPP **8** (figure 15).

Figure 15



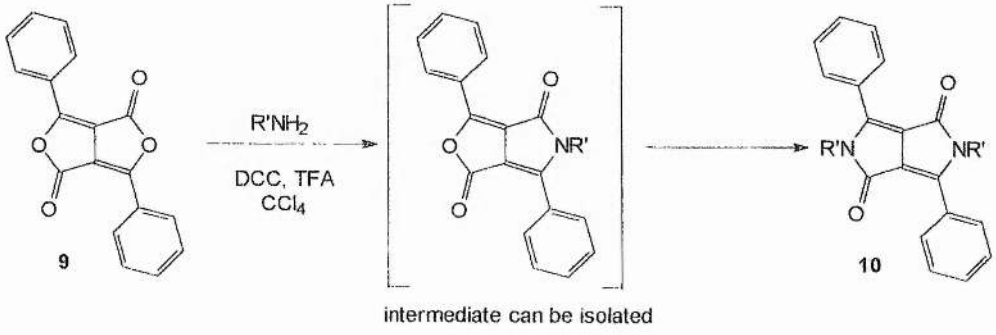
Furthermore, the reaction of succinamide with *N,N*-dimethylbenzamide diethyl acetal (figure 16) provides a further example of a DPP synthesis - a modification of the commercial synthesis from a succinate.

Figure 16



Most recently, a synthesis of *N*-arylated DPPs was disclosed, starting from the dilactone **9**. Reaction of this precursor with a primary aromatic amine in the presence of DCC furnished the soluble, fluorescent DPP dye **10** (figure 17). This provided a more efficient route to these compounds, rendering direct *N*-substitution of the normal DPP (see later, page 23) unnecessary.[32]

Figure 17

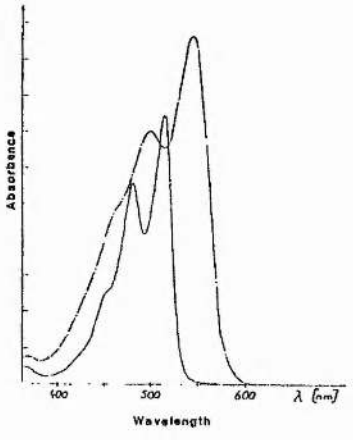


1.4 PROPERTIES OF DPP DERIVATIVES

1.4.1 Colour and electronic spectral properties

3,6-Diphenyl-1,4-diketopyrrolo[3,4-*c*]pyrrole (3,6-diphenyl-DPP) is a pigment with a pale yellow colour in solution and a vivid red colour in the solid state. There is a striking resemblance between the absorption spectra in both phases. Hence, the solid state spectrum can be viewed as the solution spectrum with a bathochromic shift (~40nm).[33-34] The dependence of colour on crystal packing (a phenomenon sometimes referred to as crystallochromy[35]) is common to a variety of pigment classes, and is clearly illustrated in the absorption spectra for the solution versus solid phases of 3,6-diphenyl-DPP (figure 18).

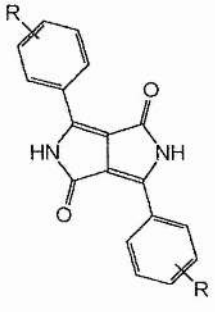
Figure 18



Absorption spectrum of diphenyl-DPP 2 (—— solution, - - - - solid)

A broad range of shades in the solid state ranging from orange-yellow to violet were accomplished simply by varying the substituents in the *m*- and *p*-positions of the two phenyl rings attached to the central DPP chromophore (figure 19).

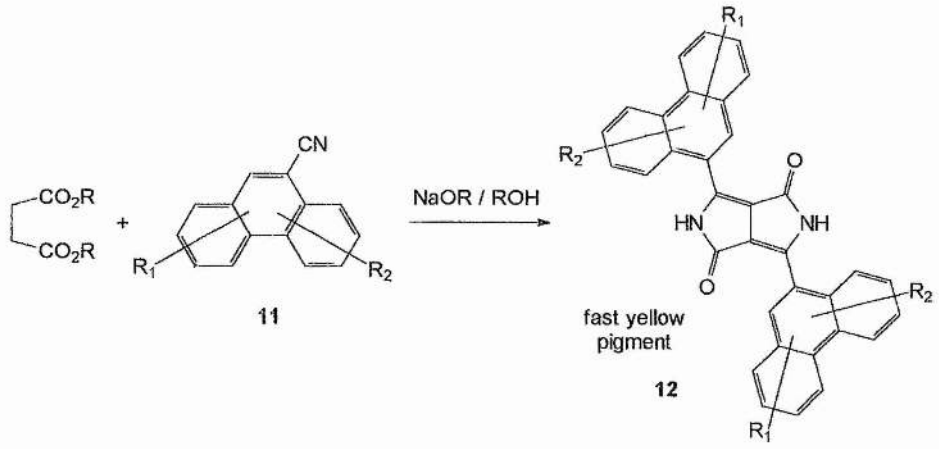
Figure 19



R	shade
H	yellow-red
m-CF_3	orange-yellow
p-CN	bordeaux
m-CCl_3	orange
m-Cl	orange
p-Br	blue-red
p-NMe_2	violet-blue

Reaction of 9-cyanophenanthrene **11** with a dialkyl succinate, employing a sodium alkoxide as base, furnished the novel DPP derivatives **12** which were found to offer fast yellow shades[36], complimenting the range of shades already achieved above (figure 20).

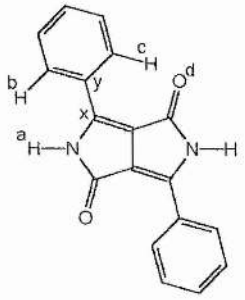
Figure 20

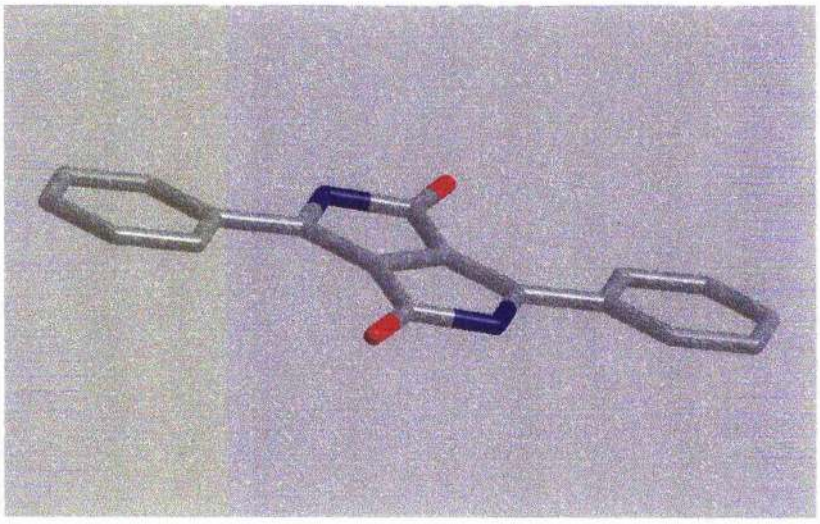


1.4.2 Structure

The crystal structure of 3,6-diphenyl-DPP has been elucidated[37] (figure 21). X-ray data show the heterocyclic chromophore unit to be essentially planar with the phenyl rings twisted in the same direction out of this plane by 7(1)°. The interatomic C_x-C_y distance is shorter than the analogous C-C single bond of biphenyl. Such bond shortening was presumed to be caused by well delocalised π-electrons in the DPP chromophore, imparting some double bond character to the C_x-C_y bond. This would further explain the influence of substituents on the phenyl rings upon the colour of 3,6-diphenyl-DPP derivatives.

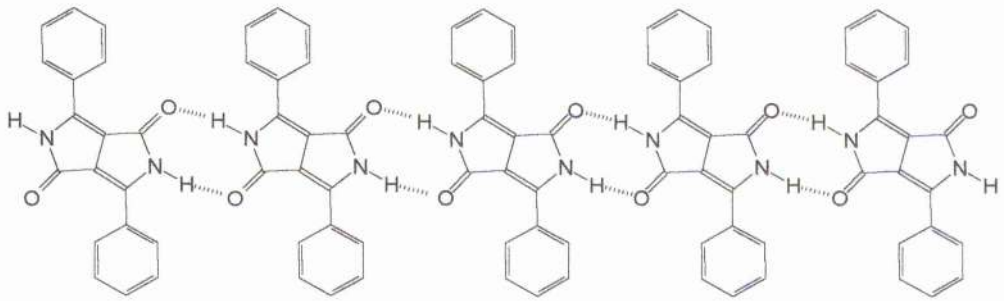
Figure 21





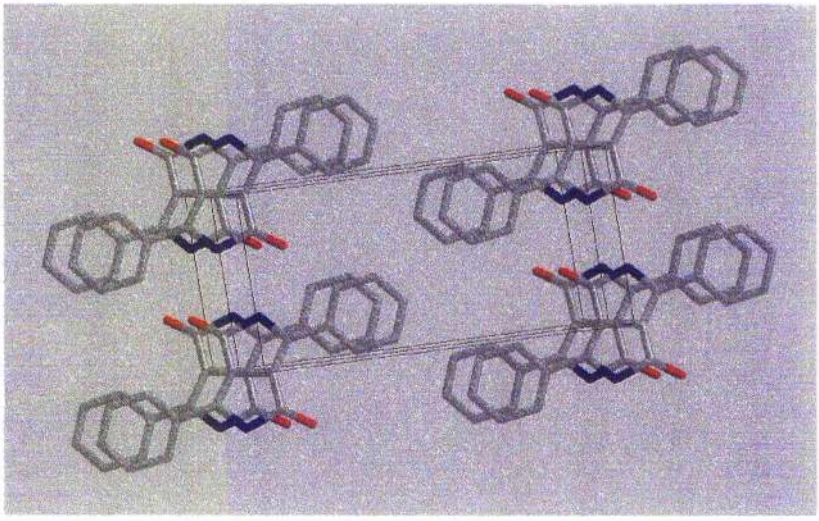
The DPP molecules are aligned in nearly the same plane, parallel to each other, with intermolecular hydrogen bonds between the amidic NH of one molecule and the amidic carbonyl of a neighbouring molecule (figure 22). Van der Waals' contact also exists.

Figure 22: H-bonded 2-dimensional network of DPP molecules



These planes of DPP molecules stack, with overlap in the central DPP heterocycles leading to π-π interactions (figure 23). The strong nature of the hydrogen bonding and the π-π interactions exclude solvent molecules and so impart a very low solubility to DPP.

Figure 23: Crystal packing diagram of 3,6-diphenyl-DPP



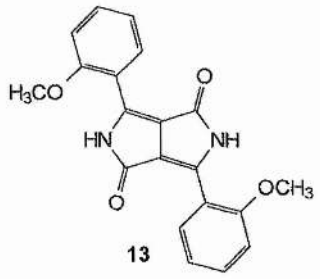
1.4.3 Influence of structure on electronic properties

The cause of the bathochromic shift from the solution to the solid phase electronic spectra in 3,6-diphenyl-DPP has been investigated from the standpoint of intermolecular hydrogen bonding between the amidic NH of one DPP molecule and the amidic carbonyl of another. In other words, the goal was to study the influence of hydrogen bonding and deprotonation on the DPP chromophore; this is different from the investigation of similar spectral shifts in other pigments[38] (e.g. perylene pigments) which focus upon molecular conformation and crystal packing effects. Such studies highlight that intermolecular hydrogen bonding in DPP involves partial electron transfer from the carbonyl oxygen atom to the NH bond in the solid state, thus increasing the electron density on the nitrogen atom. Consequently, there is more electron density within the DPP heterocycle itself, which contributes to the observed bathochromic displacement.

This shift has further been investigated by theoretical methods[39-40], namely via *ab initio* molecular orbital calculations. Ultimately, the aim was to understand how the geometry of aggregated chromophoric structures affected electronic and spectral properties - fundamental to a fuller appreciation of the colour performance properties of a pigment dispersion. These investigations provided further evidence in support of the theory that the source of the bathochromic shift was indeed the intermolecular hydrogen bond.

Furthermore, *N*-alkylated DPP derivatives were observed to show strong fluorescence, which can vary greatly from the solution to the solid phase, dependent upon which substituent is present. The relationship between crystal packing effects and the solid state fluorescence of dyes and pigments is little understood, but has been examined in the case of the di-*N*-alkylated DPP derivatives.

Figure 24



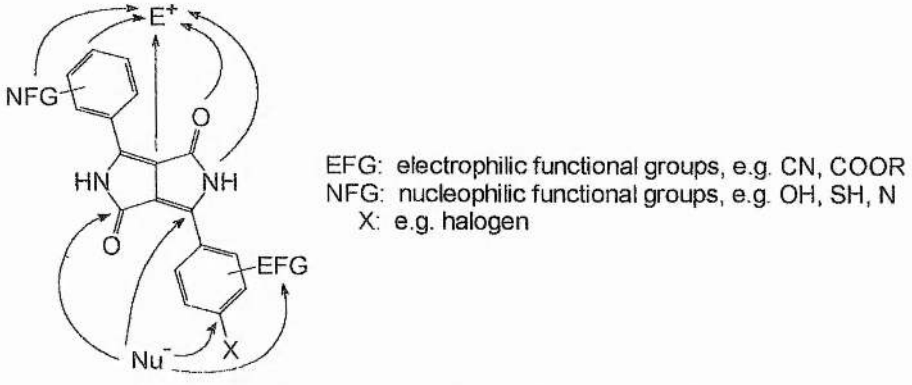
13

The DPP derivative **13** (figure 24) was highlighted as an important link between solid and solution phase fluorescence because it exists in two crystal modifications: the thermodynamically stable form **13a** shows an intense solid-state fluorescence, while modification **13b** fluoresces only weakly. The crystal structure of each modification was examined via X-ray analysis as a probe to investigate the influence of crystal packing effects on the solid state fluorescence. In both modifications, the DPP units were similarly stacked, but the marked difference was the distance between the planes of DPP heterocycles. Modification **13b** contained the DPP heterocycles aligned under one another (3.81 Å apart). Modification **13a** contained the DPP units more tightly compressed against each other so that DPP-DPP chromophore interactions could only occur with the next but one layer (6.18 Å apart). Therefore, such chromophore interactions were negligible for **13a**. It was believed that these interactions allowed deactivation of the fluorescence via a flow of the electronic excitation into lattice vibrations. Hence, in **13b** the fluorescence is weak, but remains strong in **13a** since the interactions are weak.

1.4.4 Chemical reactivity

A qualitative inspection of a diaryl-DPP molecule reveals several centres of reactivity (figure 25). The substituted phenyl rings may be expected to undergo electrophilic and possibly nucleophilic substitution reactions, whilst the central DPP heterocycle incorporates three different functional groups; carbon-carbon double bonds, carbonyl groups and NH groups. One could expect that each of these could be amenable to chemical transformation. Synthetic efforts to date have mainly focussed upon *N*-substitution and nucleophilic transformations of the carbonyl groups without concurrent rupture of the DPP heterocycle. In most cases synthetic efforts have been targeted to exploit the chemical reactivity so as to provide DPP derivatives of improved pigment performance or of novel application properties which would otherwise be difficult to prepare. The basic chemistry of DPP materials was investigated extensively by the group at Ciba-Geigy and reviewed in the literature by A. Iqbal *et al.*, but will be included for completeness in this review before moving on to discuss recent developments in the field.

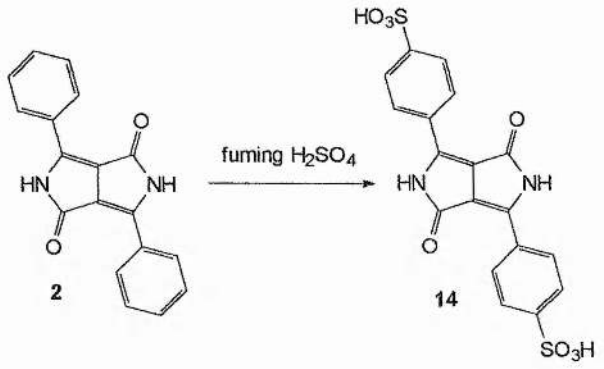
Figure 25: Centres of potential reactivity in the diaryl-DPP molecule



(taken from A. Iqbal, M. Jost, R. Kirchmayr, J. Pfenninger, A. Rochat and O. Wallquist[18])

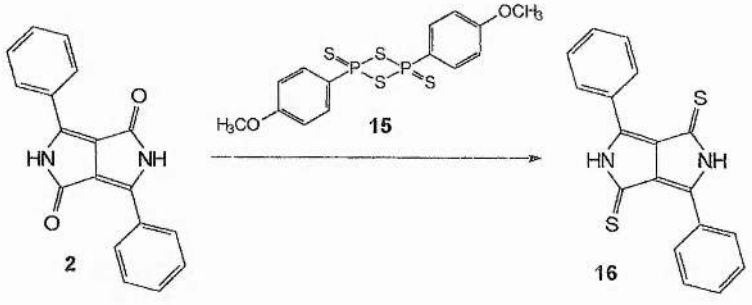
Electrophilic aromatic substitution was readily accomplished; for example, sulfonation with fuming sulfuric acid to provide the disulfonic acid derivative **14** (figure 26). Such a water-soluble derivative may be readily converted to a group 2 metal salt which may be useful for improving the dispersion of DPP pigments within paint media.[43] Ultrathin DPP multilayer films which are deeply coloured have recently been prepared via electrostatic self assembly of sulfonated DPP derivatives, demonstrating their usage as excellent surface pretreatment agents.[44]

Figure 26: Sulfonation of 3,6-diphenyl-DPP



The aromatic halogenation of 3,6-diphenyl-DPP **2** did not proceed as readily as the sulfonation reaction, leading instead to rupture of the central DPP heterocycle. Only in the case of direct bromination was any halogenated product isolated as expected. Transformation of the amidic carbonyl group of DPP without cleavage of the heterocycle itself was attempted with oxygen, sulfur and carbon nucleophiles. Only in the case of sulfur was this direct conversion possible: reaction of 3,6-diphenyl-DPP with Lawesson's reagent **15** yielded the 3,6-diphenylpyrrolo[3,4-*c*]pyrrole-1,4-dithione (DTPP) derivative **16** (figure 27).[45]

Figure 27: Thionation of DPP using Lawesson's reagent

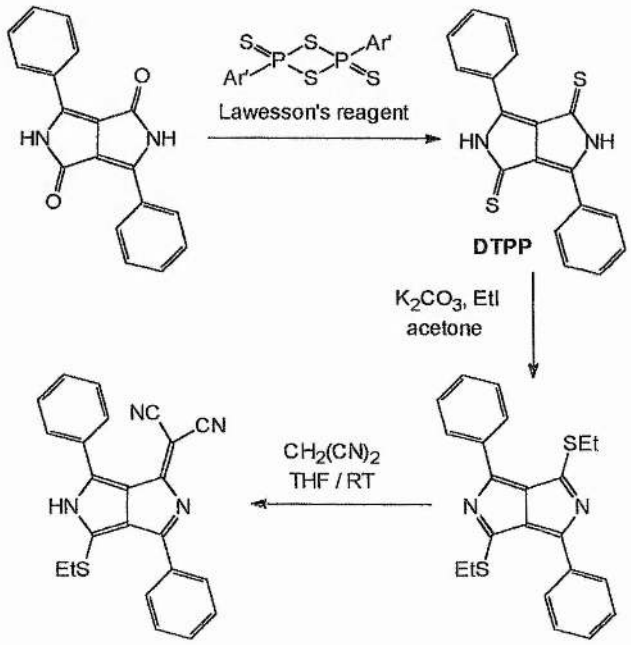


Thionation of the DPP heterocycle was shown to bring about an intense near-IR absorption in the solid state. For this reason, derivatives of this sort have been the subject of extensive investigation, attracting attention for potential electrophotographic applications.[46-52] Their suitability for use as materials in laser printers and in optical information storage systems has been of particular importance. Three crystal modifications of 3,6-diphenyl-DTPP are known, only one of which exhibits near-IR absorption. This difference between the phases has been developed to

provide a 'write once' type optical information storage system which is now used within compact disc devices.

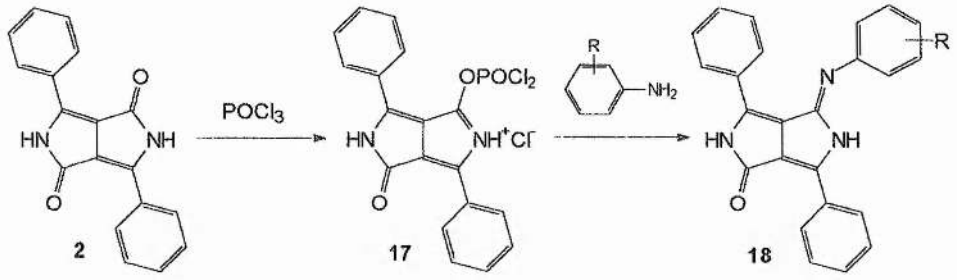
To achieve replacement of the carbonyl oxygen by carbon, the DTPP was employed as a more suitable substrate for reaction with carbanions. The base promoted reaction with ethyl iodide and subsequent reaction with a suitable carbon nucleophile (figure 28) demonstrates such an approach.[53]

Figure 28: Replacement of O by C in 3,6-diphenyl-DPP



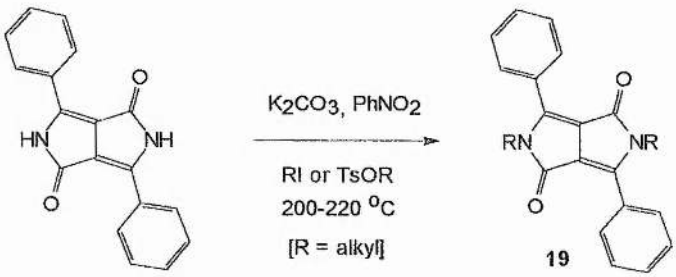
To replace the carbonyl oxygen by nitrogen, prior conversion of the carbonyl group to a functionality more amenable to reaction with nitrogen centred nucleophiles was required. The reaction of 3,6-diphenyl-DPP with phosphoryl chloride provided the stable phosphorylated product **17** which readily underwent reaction with aromatic amine nucleophiles to yield the novel DPP derivatives **18** (figure 29).[51] Thus, replacement of the carbonyl oxygen using sulfur, carbon and nitrogen nucleophiles was accomplished.

Figure 29: Replacement of O by C via a phosphorylated DPP intermediate



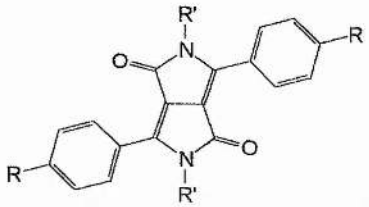
Alkylation of the DPP heterocycle was achieved via reaction with an alkyl halide or alkyl sulfonate in the presence of potassium carbonate, employing a suitable high boiling or dipolar aprotic solvent (such as nitrobenzene or DMF) at high temperature to ensure suitable dissolution of the highly insoluble pigment reagent.[55-56] In every case, *N*-alkylation was achieved with no *O*-alkylation products observed (figure 30). The products **19** obtained were photostable, fluorescent dyes with high solubility in common organic solvents, the solubility being attributed to the loss of intermolecular hydrogen bonding. The fluorescence varies dependent upon the substituents in place.

Figure 30 : *N*-alkylation of DPPs



Most recently, the DPP heterocycle has been introduced into liquid crystal research using an *N*-substitution approach in which 3,6-diaryl-DPP derivatives **20** were prepared with the aryl groups bearing long chain alkyl substituents and then were solubilised via *N*-alkylation (figure 31).[57] This initial research has demonstrated the development of DPP materials which exhibit either a nematic or smectic A phase and offers promise for the future development of coloured liquid crystal materials.

Figure 31: Coloured liquid crystal materials



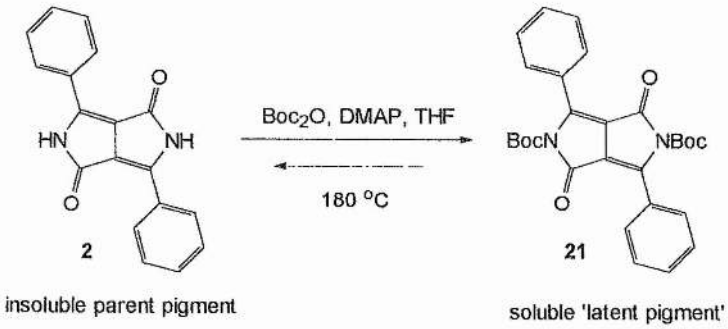
20

R	R'
$H_{25}C_{12}O$-	CH_3
$H_{13}C_6O$-	CH_3
H_9C_4-	CH_3
H_7C_3-	CH_3
$H_{11}C_5$-	CH_3
$H_{11}C_5$-	C_2H_5

In addition, the fluorescence of *N*-alkylated DPP derivatives has been used as a handle to investigate single dendrimer macromolecules: a dendrimer with a DPP chromophore at its core was prepared and the fluorescence measured to distinguish single molecules from small dendrimer clusters.[58]

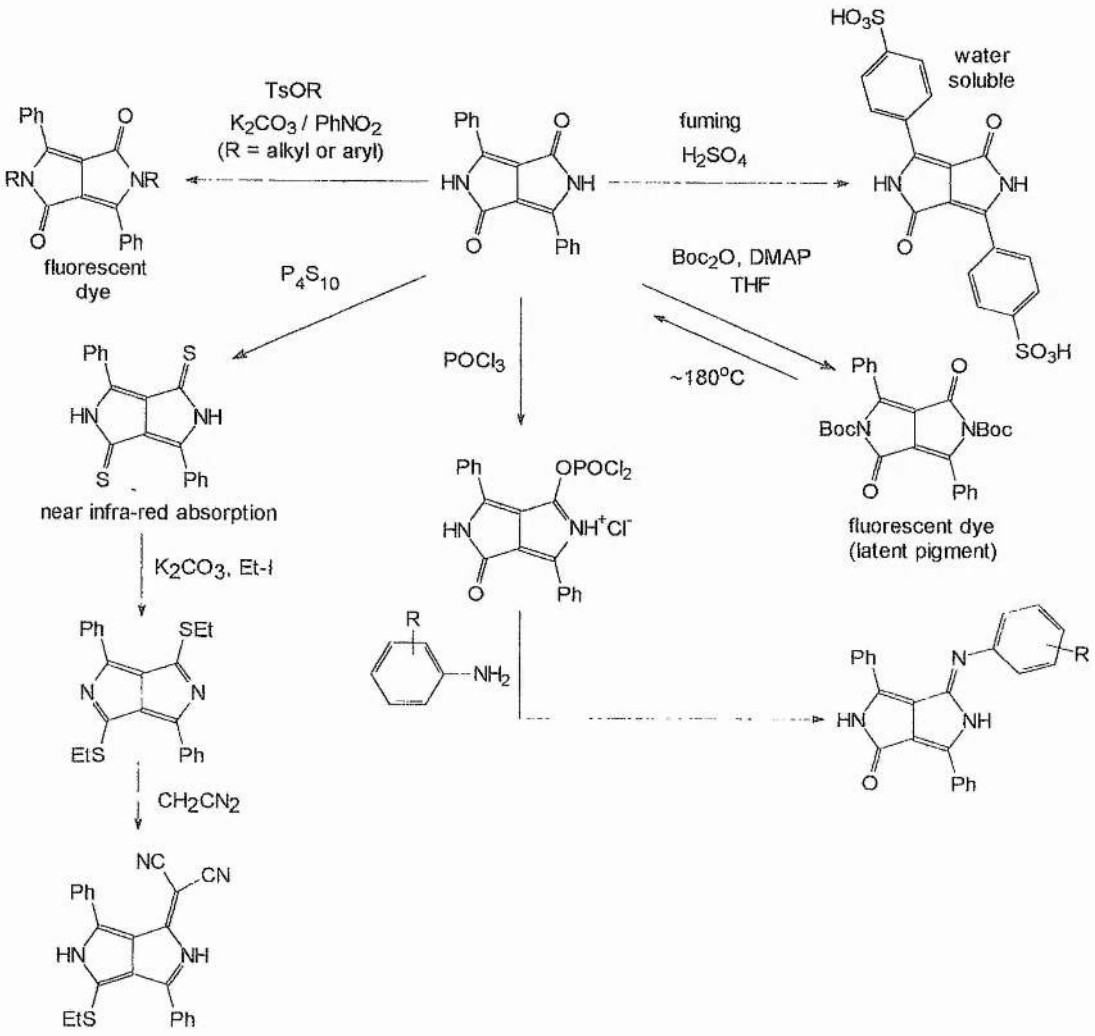
The amidic NH groups can be readily protected as a *t*-butoxycarbonyl derivative under standard conditions. For example, reaction of 3,6-diphenyl-DPP **2** with di-*t*-butyl dicarbonate in a suitable solvent such as THF, employing 4-(*N,N'*-dimethylamino)pyridine as catalyst, yielded *N,N'*-bis-(*t*-butoxycarbonyl)-3,6-diphenyl-1,4-diketopyrrolo[3,4-*c*]pyrrole **21** in high yield under mild conditions (figure 32). Unlike its parent pigment the product **21** is readily soluble in common organic solvents. This simple reaction provides a much more valuable product than first realised: the soluble, *N*-Boc protected derivative can be easily dispersed in an application medium and then regenerated via subsequent thermal treatment at approximately 180 °C. This process offers significant advantages for pigment technology because it simplifies the application process but still allows a homogeneous distribution of pigment particles in a substrate.[59]

Figure 32: Preparation of a 'latent pigment' via *N*-Boc protection strategy



The general developments in DPP chemistry are summarised below.

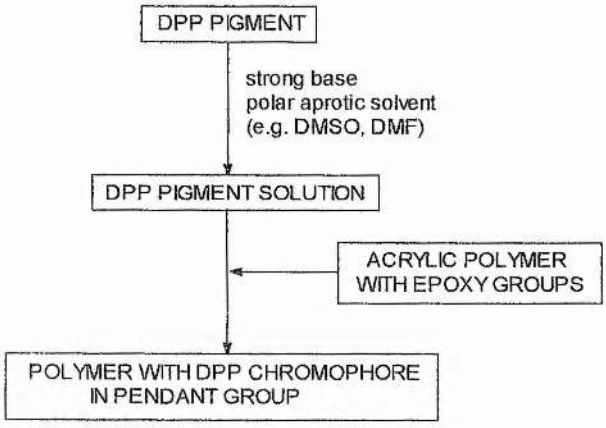
Figure 33: Summary of DPP chemistry



1.4.5 Polymerisation of DPPs

DPP pigments have been incorporated as pigment additives into plastic materials in order to modify the optical properties of the product, so enhancing their market appeal.[60] In this instance, the pigment is dispersed into the polymer in its liquid phase, with retention of the pigment particles within the polymer matrix upon solidification. By contrast, *N*-substituted DPP derivatives may be employed as dye-based additives for plastics and as such dissolve more or less completely in the polymeric application medium. However, these are merely additive approaches to colouration of polymers and do not employ novel polymerisation chemistry. The first communication which reports chemical attachment of the DPP molecule to the polymer describes polymers having DPP as a pendant group,[61] readily prepared from the DPP dianion via reaction with pendant epoxy groups within the polymer. These materials were used in paint systems as a dispersant for organic pigments (figure 34). Similarly, the grafting of living polymer cations [e.g. poly(isobutyl vinyl ether)] with DPP has recently been reported to change the wettability of the pigment surface.[62]

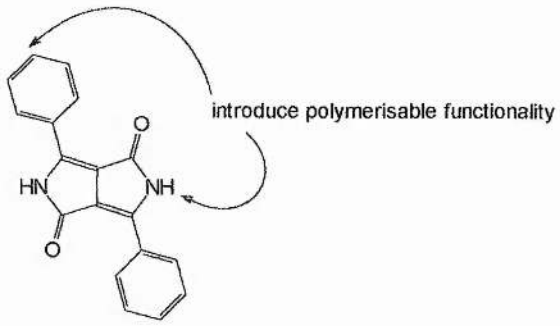
Figure 34



Incorporation of the DPP chromophore into polymer chains poses quite a different challenge and would ultimately yield interesting novel types of deeply coloured and fluorescent polymers. At the present time, surprisingly little effort has been undertaken to incorporate the DPP chromophore chemically into a polymer chain and only a limited number of examples of such work have reached the published literature. In all these examples, efforts have been targeted at introducing functional groups amenable to polymerisation either at the nitrogen of the lactam groups or at

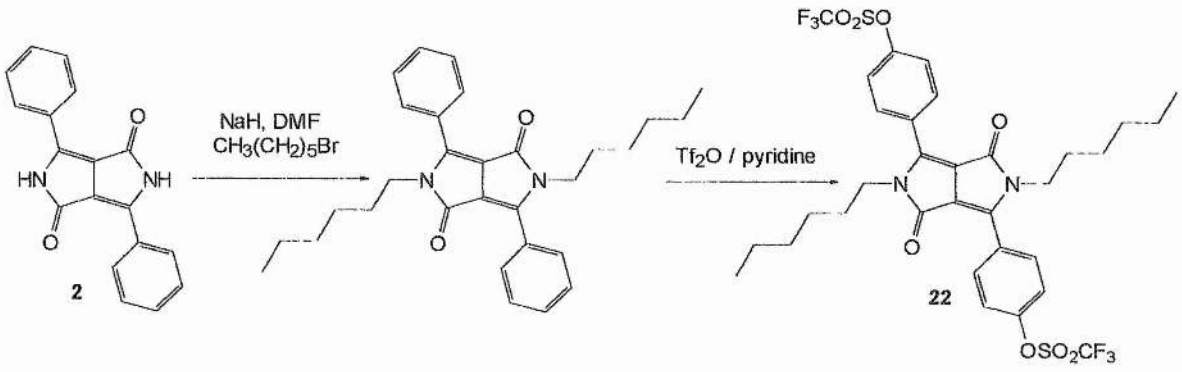
the 4-position of the phenyl groups. In both cases the central DPP heterocycle was retained intact (figure 35).

Figure 35



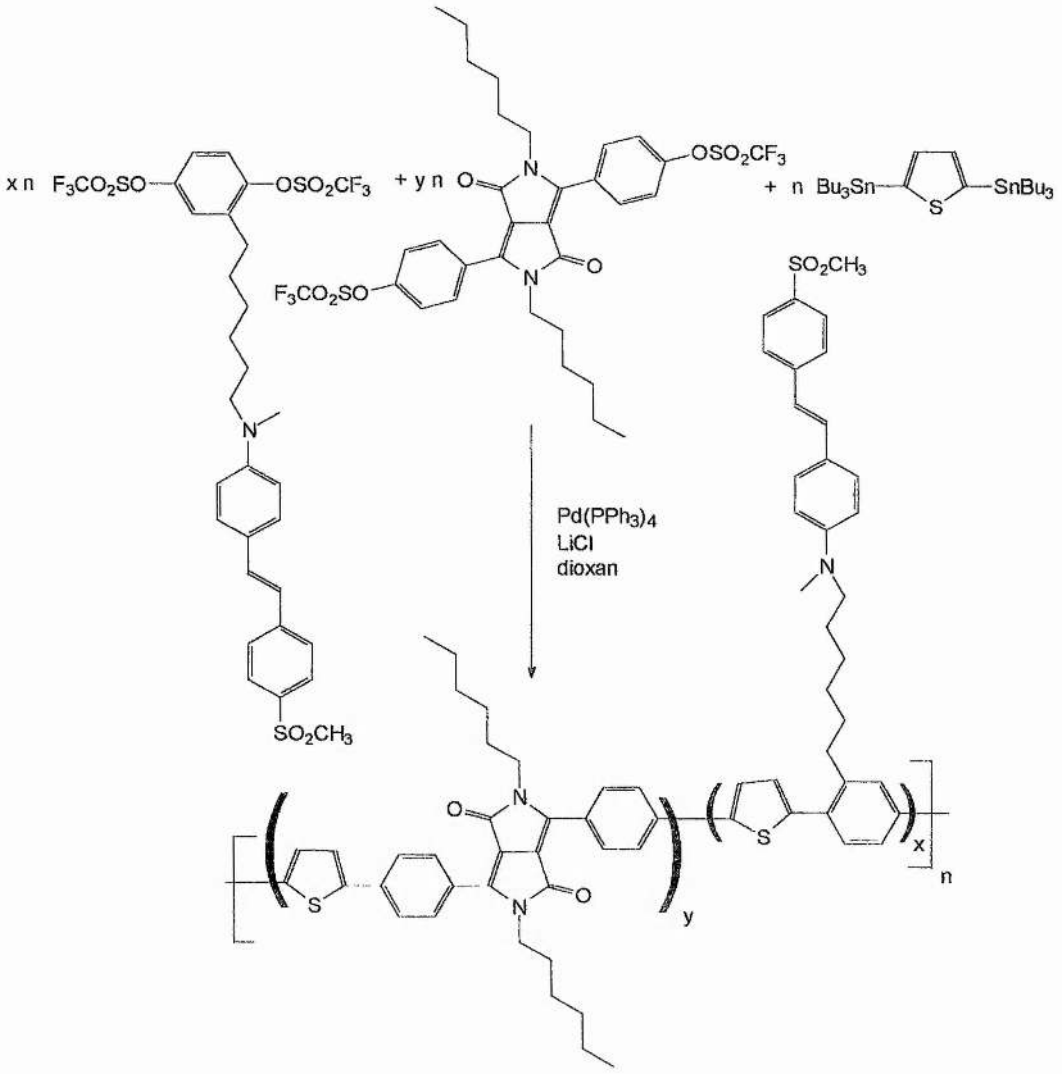
The only example detailing the introduction of polymerisable groups in the 4-position of the phenyl groups entailed aromatic substitution to prepare bifunctional monomeric DPP derivatives **22** (figure 36).[63-64]

Figure 36: Preparation of monomers for Stille coupling polymerisation



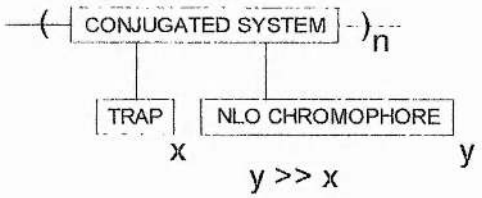
The monomers **22** were then polymerised via a Stille coupling[65] reaction to provide products which were photorefractive polymers (i.e. multifunctional polymers which also possess photoconductivity and electro-optical activity). This method of polymerisation employed mild conditions and was tolerant to different functionalities within the monomer (figure 37).

Figure 37: Stille coupling reaction to yield photorefractive polymer product



To manifest photorefractive properties a polymer must possess: (a) a photocharge generator, (b) a charge transporter, (c) a charge trapping centre and (d) a nonlinear optical (NLO) chromophore (figure 38). In the example outlined here the polymer backbone functions as both the charge generator and transporter.

Figure 38: Schematic structure of a conjugated photorefractive polymer

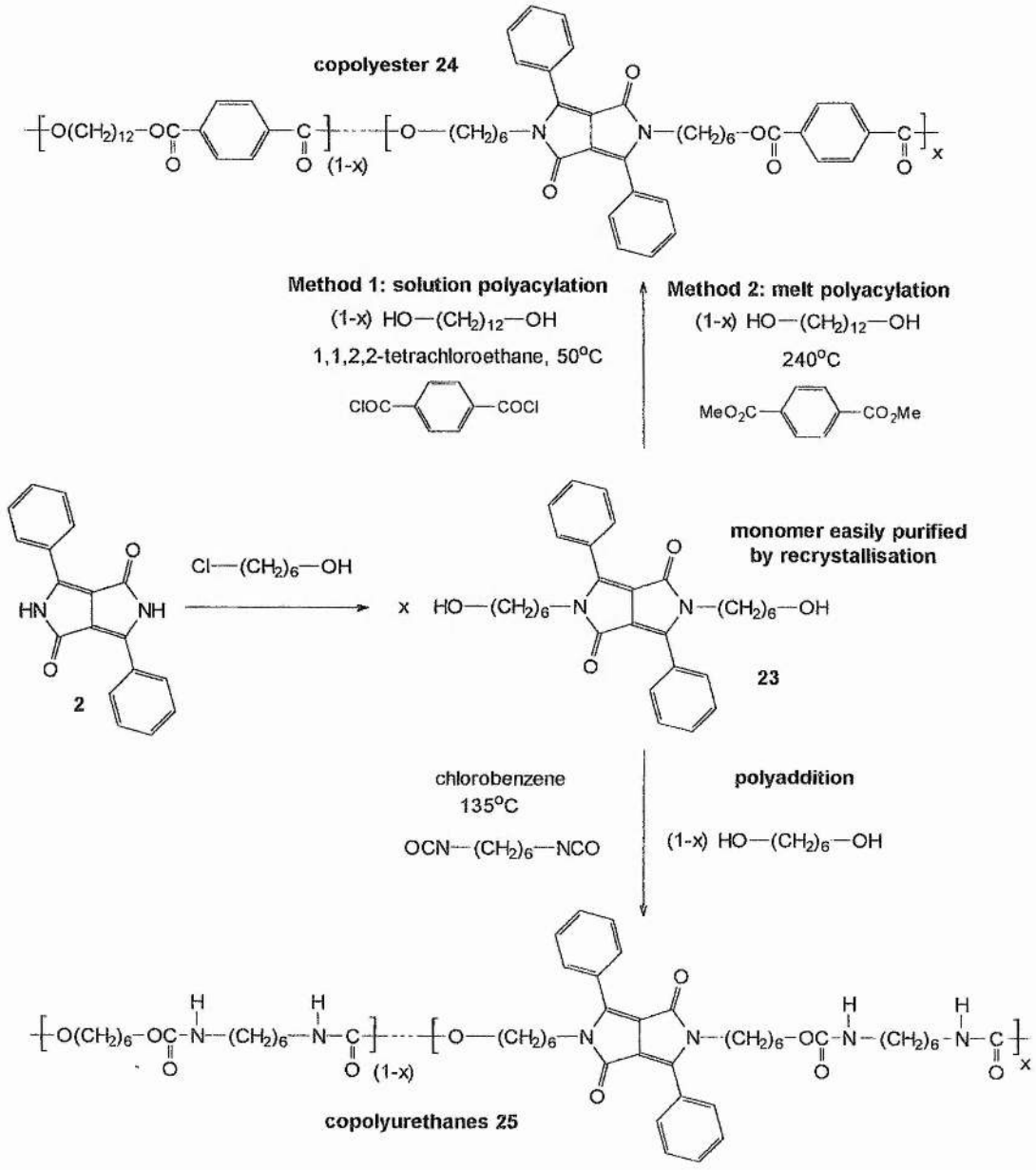


The all-important incorporation of the DPP unit into the polymer allows a means by which to control the absorption strength of the polymer at specific regions in the UV-visible spectrum.[66] The driving force behind investigations into photorefractive polymers has been their potential application - the handling of large quantities of information in real time (i.e. data storage). However, research in this area is still very much in its infancy.

The only published example of a polymerisation approach which employs the introduction of functional groups on the nitrogen of the DPP moiety was reported recently. A monomer **23** was prepared from the parent DPP molecule **2** via *N*-alkylation with 6-chlorohexanol. Using established polyacylation and polyaddition procedures, the monomer **23** was easily polymerised to afford copolyesters **24** and copolyurethanes **25** with the DPP chromophore chemically incorporated into the main polymer backbone (figure 39).[67]

Due to the presence of rigid, anisotropic DPP units in the flexible polymer backbone, liquid crystalline properties were anticipated in these final products. In practice it was observed that the overall crystallinity of the polymer was reduced as the DPP content of the polymer was increased, but no evidence supporting the existence of liquid crystalline phases and the anisotropic ordering of the DPP units could be found. This was attributed to the the *N*-substitution approach which leads to destruction of the hydrogen bonding between the DPP lactam units (other approaches to incorporating the DPP heterocycle into liquid crystals were discussed earlier). However, the optical properties of these polymers are very interesting: yellow to red solids were obtained which could be readily processed and all the polymers exhibited brilliant colours, the brilliance originating from a strong solid-state fluorescence.

Figure 39: Polymerisation of DPP based monomers using established procedures



As described above, the chemistry of DPP is diverse and has been exploited for improving the pigment performance and for incorporating the heterocycle into novel materials (e.g. liquid crystals and polymers).

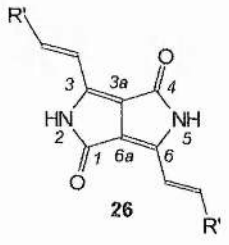
1.5 AIMS AND OBJECTIVES - NOVEL ALKENYL-DPPs

1.5.1 Background

There is a continual drive to develop DPP derivatives of improved pigment performance or for novel applications. The chemistry of DPP has been reviewed in the Introduction and has been exploited to provide a diverse range of DPP materials. Incorporation of the DPP heterocycle into polymer chains poses a real challenge and would ultimately yield novel types of deeply coloured and fluorescent polymers. At the present time, surprisingly little effort has been undertaken to chemically incorporate the DPP heterocycle into a polymer chain: only a limited number of examples of such work have reached the published literature (for details see section 1.4.5). In both cases, the central DPP heterocycle is retained intact, but the amidic hydrogen is removed, thus removing any possibility of hydrogen bonding

If substituents incorporating an alkenic double bond could be introduced through the 3- and/or 6- positions of the DPP heterocycle (figure 40), such materials may prove amenable to free radical polymerisation reactions. This could yield polymers with the DPP heterocycle chemically incorporated into the polymer backbone whilst retaining the amidic hydrogen atoms of the DPP heterocycle. It may therefore be possible to maintain a degree of hydrogen bonding between the DPP moieties within the polymer.

Figure 40: Alkenyl-DPPs



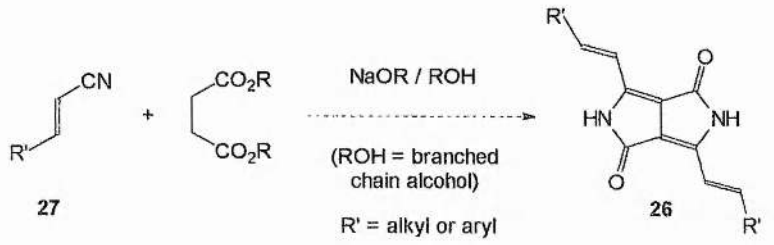
26

The alkenyl-DPPs **26** are hitherto unknown compounds and so demand new synthetic methods.

1.5.2 DPP precursors and novel methods for their synthesis

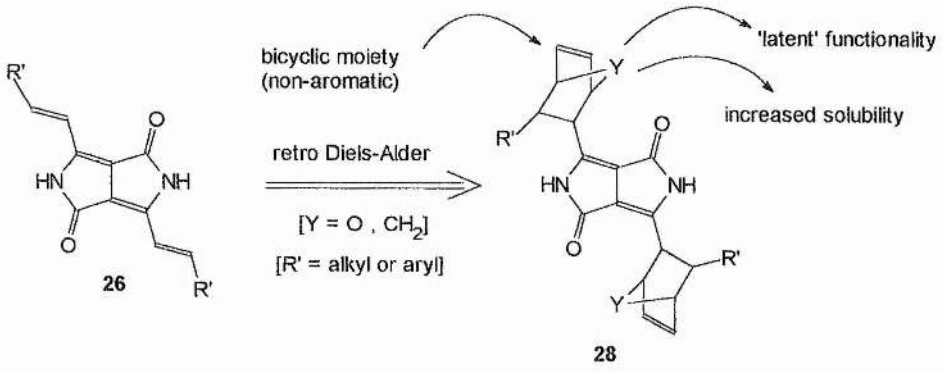
To prepare alkenyl-DPP derivatives of type **26** one would first envisage a reaction similar to the commercial synthesis of 3,6-diphenyl-DPP **2** (figure 41), comprising the reaction of a succinic ester with an α,β-unsaturated nitrile **27**. However, a nitrile such as **27** is also an excellent Michael acceptor, and so it was recognised that conjugate addition of the lactam ester anion may occur in addition to, or in preference to, 1,2-addition to the nitrile functionality. These side reactions could also make purification of any DPP product difficult if a mixture of insoluble products was obtained.

Figure 41: Possible synthesis route to alkenyl-DPPs



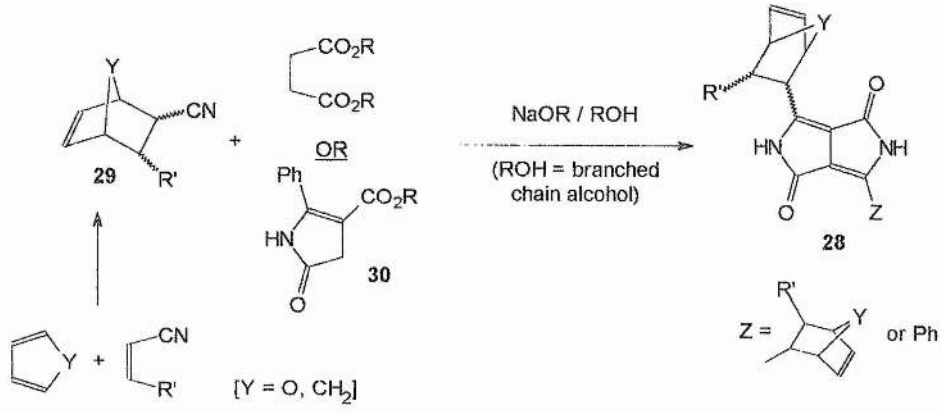
Instead, the necessary carbon-carbon double bond could be introduced via a retro Diels-Alder strategy (figure 42) wherein a latent alkenic double bond is incorporated into the structure by preparing alkenyl-DPP precursors of the type **28**. These precursors may be interesting in themselves. They are not fully conjugated systems, lacking aromatic substituents in the 3- and/or 6-positions of the DPP heterocycle, and the π-π stacking of the DPP heterocycles within the crystal structure may be disturbed by the bulky, non-planar substituents, leading to unusual solubility properties. The bicyclic moieties may also be amenable to a number of different chemical transformations (e.g. aromatisation, ROMP) and this may allow the preparation of hitherto unknown DPP derivatives in addition to, or instead of, the desired alkenyl-DPPs.

Figure 42: Retrosynthetic analysis for alkenyl-DPPs



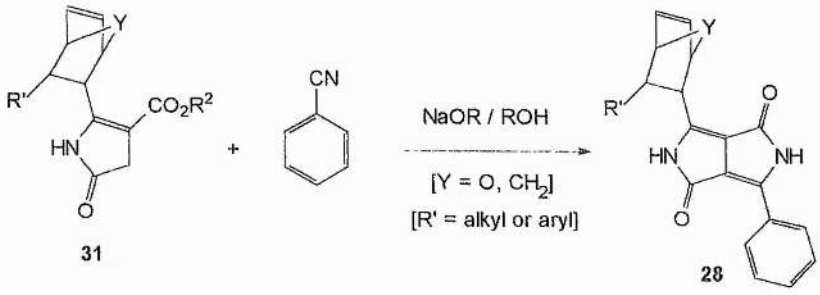
Several possible strategies for the synthesis of alkenyl-DPP precursors **28** are evident. Firstly, a DPP synthesis starting from a nitrile **29** and either a succinic ester or the corresponding lactam ester **30** (figure 43) could be adapted for this special case. This would directly afford symmetrical and unsymmetrical alkenyl-DPP precursors **28**.

Figure 43: DPP precursors via traditional synthesis methods



Secondly, the independent synthesis of a lactam ester intermediate **31** (figure 44) with the necessary bicyclic moiety already incorporated would allow access to the desired alkenyl-DPP precursors **28** upon reaction with a suitable nitrile (e.g. benzonitrile as shown).

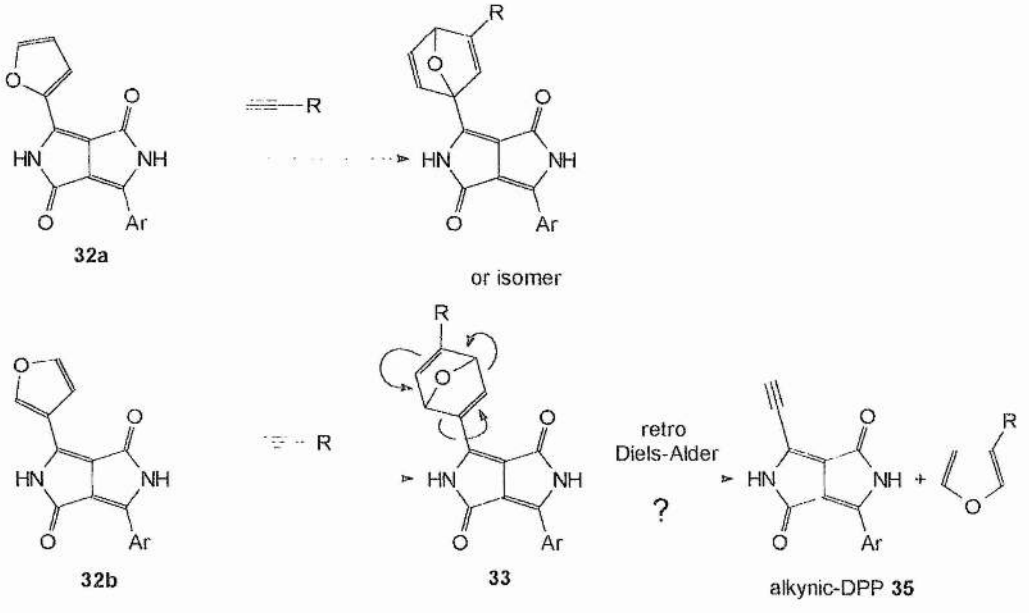
Figure 44: Lactam ester intermediate with bridged bicyclic substituent



1.5.3 Furyl-DPPs

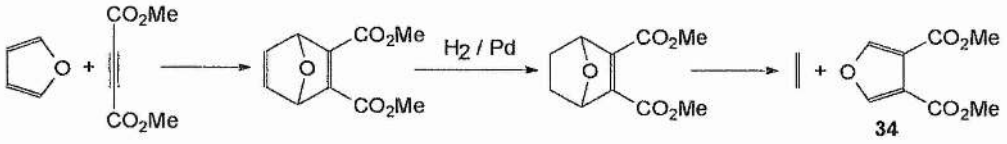
In addition to alkenyl-DPPs of type **26** (figure 40), it was envisaged that dienyl-DPPs of type **32a** and **32b** (figure 45) could be useful alkenyl-DPPs of a different type. Such compounds could undergo Diels-Alder reactions with suitable dienophiles. The Diels-Alder reaction of polymers that contain furan moieties has been reported by Laita *et al.*[68] and in particular the reaction of the furan moiety with a suitable bis-dienophile has been described. Ultimately, it was envisaged that polymerisation of the dienyl-DPP monomers **32a** and **32b** could be achieved via a Diels-Alder reaction with a bis-dienophile.

Figure 45



Furthermore, the Diels-Alder reaction of furan with DMAD followed by a selective hydrogenation of the adduct then a retro Diels-Alder reaction is reported to provide ethylene and dimethyl furan-3,4-dicarboxylate **34** (figure 46).[69] It was envisaged that the Diels-Alder adduct **33** of the 3-furyl-DPPs might undergo a similar retro Diels-Alder reaction, either spontaneously or on heating, to release an alkynic-DPP product **35** (figure 45).

Figure 46: Literature example



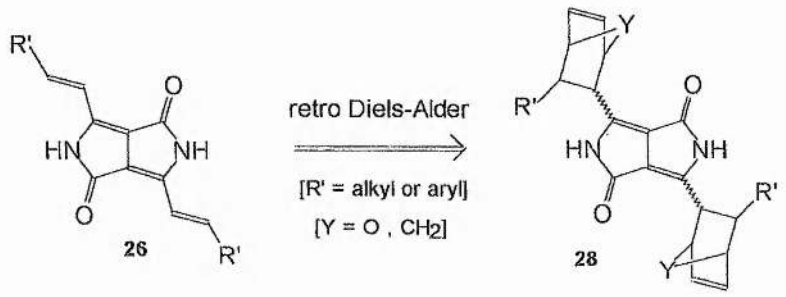
Chapter 2

THE PREPARATION OF ALKENYL-DPP MONOMERS

2.1 Introduction

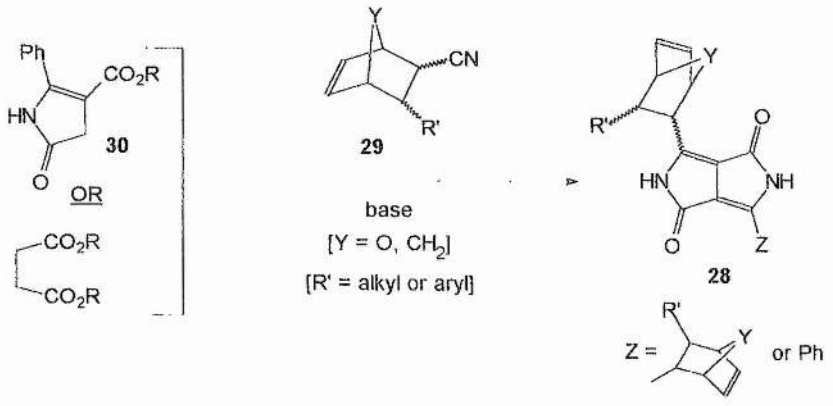
In Chapter 1 the potential use of alkenyl-DPPs **26** as monomers for free-radical polymerisation reactions was introduced (section 1.5, page 31). Several methods were proposed for their synthesis and a strategy whereby the alkenic functionality might be introduced via a retro Diels-Alder reaction was outlined (figure 47). It was intended that the concept of introducing a latent alkenic double bond to the DPP heterocycle by this means could be established.

Figure 47 : Initial synthetic target



The challenge, therefore, was to prepare the precursors of type **28**. It was envisaged that reaction of a suitable nitrile **29** (prepared via a Diels-Alder reaction) with either a dialkyl succinate or the lactam ester **30** (figure 48) would afford the desired precursors directly in a standard DPP synthesis.

Figure 48: Proposed synthesis of DPP precursors

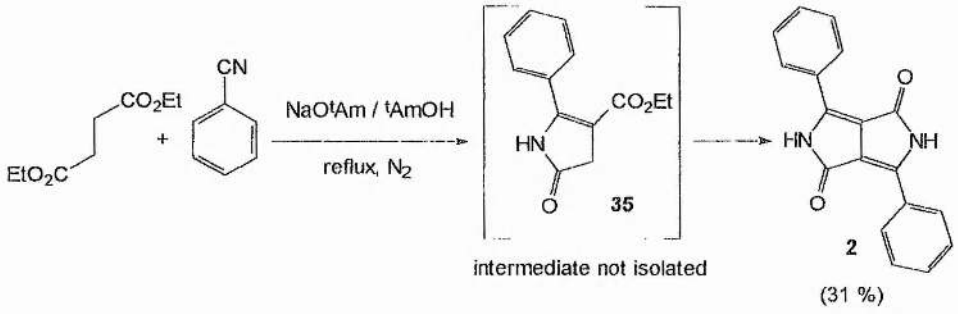


Literature methods for the synthesis of diphenyl-DPP were first completed as model reactions so that reference samples could be prepared. The synthesis of 3,6-diphenyl-DPP is now described (an adaptation of published chemistry) before moving on to discuss the novel experimental work undertaken towards the corresponding synthesis of alkenyl-DPP precursors **28**.

2.1 Synthesis of 3,6-diphenyl-DPP (literature methods)

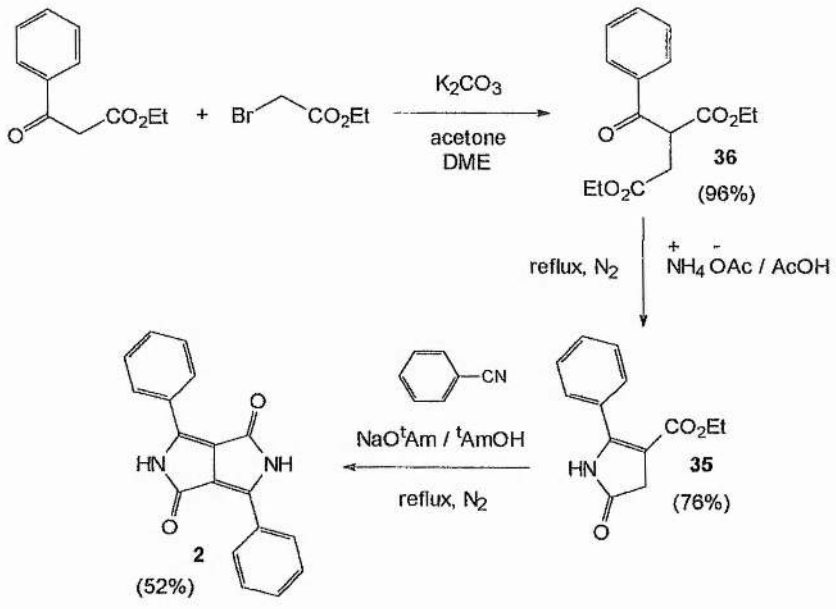
The commercial synthesis of diaryl-DPPs entails the reaction of a succinic ester with an aromatic nitrile as discussed in Chapter 1 (section 1.3.3). The reaction of diethyl succinate with benzonitrile in sodium *t*-amyloxide[18,26-27] (figure 49) was completed to yield 3,6-diphenyl-DPP **2**. The use of a *t*-alkoxide as base was described in the literature to minimise nucleophilic attack at the nitrile functionality, and a low steady-state concentration of diethyl succinate was maintained to reduce the possibility of self-condensation in the manner of Claisen acylation. A red, highly insoluble product was isolated in low yield (31%); the experimental conditions were not optimised.

Figure 49: Model reaction for synthesis of 3,6-diphenyl-DPP



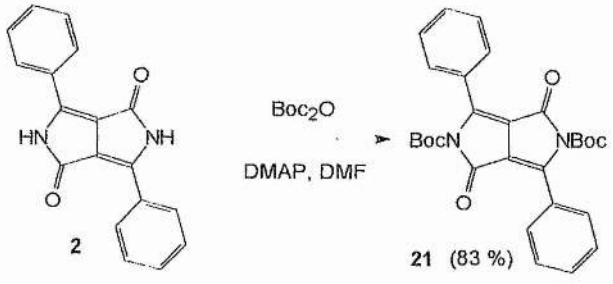
The intermediate in this reaction is the pyrrolinone ester **35**. This was also independently synthesised: diethyl benzoylsuccinate **36** was prepared in high yield from the reaction of ethyl benzoylacetate with ethyl bromoacetate and the crude product underwent ring closure upon treatment with an ammonia equivalent (in this case, ammonium acetate in acetic acid), furnishing the lactam ester **35**.[30-31] This compound was employed as a starting material in many of the syntheses discussed below. The reaction of this lactam ester **35** with benzonitrile in sodium *t*-amyloxide under nitrogen directly afforded 3,6-diphenyl-DPP **2** in moderate yield (figure 50).[18]

Figure 50: Synthesis of 3,6-diphenyl-DPP from a lactam ester intermediate



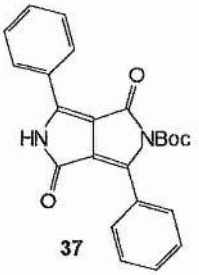
3,6-Diphenyl-DPP **2** cannot be characterised by NMR analysis because of its very low solubility in common organic solvents. Instead, only the normal complement of mass spectral and infra-red analysis was possible. To confirm the structure, methods were required to prepare a soluble derivative so that normal NMR studies could be completed. The *N*-substitution of DPP derivatives has been discussed in Chapter 1 (section 1.4.4), wherein the hydrogen bonding is removed upon substitution. This renders the *N*-substituted DPP derivatives soluble in common organic solvents. The *N*-alkylation reaction requires high temperature and is effectively irreversible. The *N*-Boc protection of DPP derivatives, by contrast, proceeds under mild conditions and the parent pigment can be easily regenerated if required. Therefore, it is useful when studying DPP pigment chemistry to employ *N*-Boc protection as a tool in the laboratory to allow the characterisation of novel DPP derivatives via NMR spectroscopy.[59]

Figure 51: Solubilisation of DPP



To demonstrate this methodology and test the conditions before proceeding with novel chemistry, the *N*-Boc protection of 3,6-diphenyl-DPP **2** was completed. Synthesis of 2,5-bis-*t*-butoxycarbonyl-3,6-diphenyl-DPP **21** was attempted by reaction of 3,6-diphenyl-DPP **2** and di-(*t*-butyl) dicarbonate in DMF under DMAP catalysis (figure 51). A soluble orange-red product, obtained in low yield (7 %), was characterised by ^{1}H and ^{13}C NMR as the 2-*t*-butoxycarbonyl-3,6-diphenyl-DPP derivative **37** (figure 52) rather than the desired product.

Figure 52



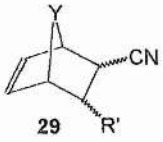
37

The 2,5-bis-*t*-butoxycarbonyl-3,6-diphenyl-DPP **21** was prepared instead by employing tetrahydrofuran rather than DMF as solvent in the above reaction. A highly soluble, solid yellow product was obtained in high yield (83 %) and characterised by ^{1}H and ^{13}C NMR. The necessary model reactions and procedures were now established so that novel chemistry leading to the preparation of the alkenyl-DPP precursors **28** could be investigated.

2.3 Nitriles from Diels-Alder chemistry

The synthesis of suitable nitriles such as **29** (figure 53) for use as reagents in subsequent DPP preparation was required.

Figure 53: Suitable nitriles for preparation of alkenic DPP precursors



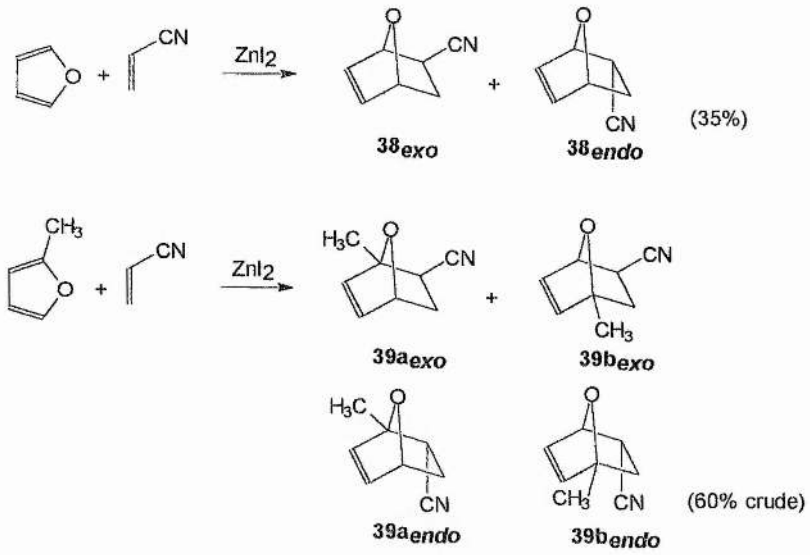
29

[Y = O, CH_2]

[R' = alkyl or aryl]

7-Oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile **38** was prepared by the Lewis acid (zinc iodide) catalysed Diels-Alder reaction of furan with acrylonitrile at atmospheric pressure (figure 54).[70] An *endo/exo* mixture of two isomers was obtained in moderate yield. Similarly, the Diels-Alder reaction of 2-methylfuran with acrylonitrile[71] (figure 54) yielded the methyl substituted adduct mixture **39**; this constituted of two constitutional isomers, each an *exo/endo* mixture.

Figure 54: Preparation of nitriles via Diels-Alder chemistry



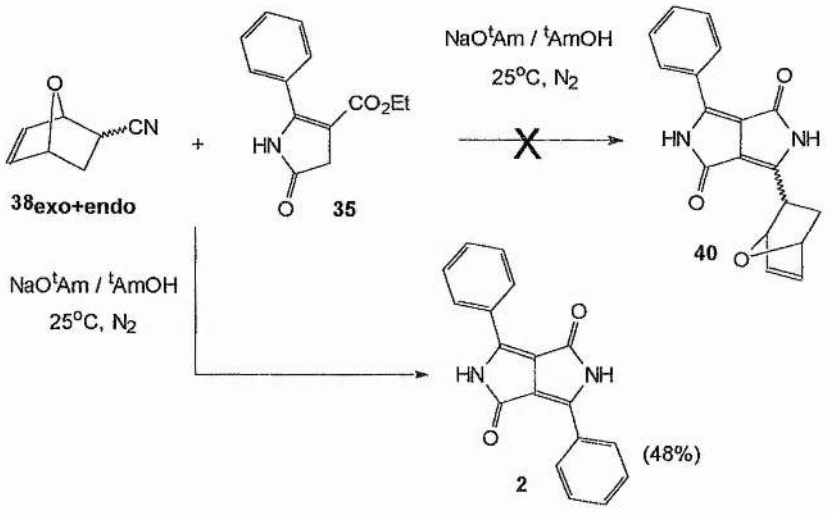
The analogous carbon-bridged nitrile, 5-norbornene-2-carbonitrile was acquired as a commercial sample: this again was an *exo/endo* mixture.

2.4 Synthesis of alkenyl-DPP precursors

2.4.1 Furan derived nitriles

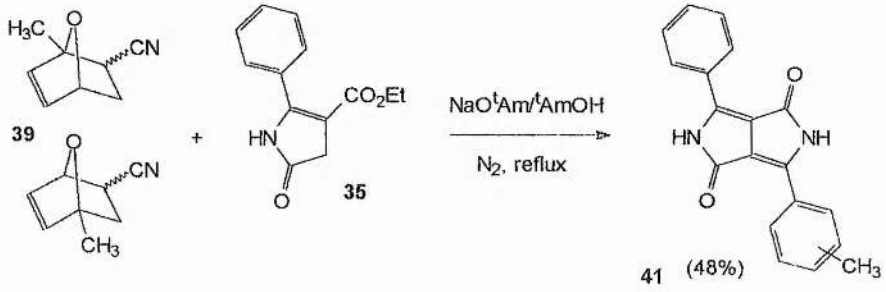
The synthesis of precursors to the alkenyl-DPPs was then attempted via reaction of the lactam ester **35** with a pre-prepared nitrile. However, the reaction of 7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile **38** with the lactam ester **35** in sodium *t*-amyloxide (figure 55) did not afford the desired alkenyl-DPP precursor **40** but rather 3,6-diphenyl-DPP **2**, with recovery of some unreacted starting material. This interesting result prompted an investigation of the mechanistic pathway of the reaction, not least because it appeared to offer a novel synthesis of diaryl-DPPs.

Figure 55: A novel synthesis of diphenyl-DPP



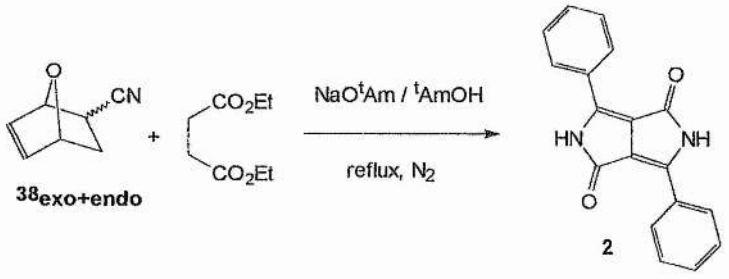
One must first consider the source of each phenyl moiety in the observed product **2** and establish whether the nitrile **38** is actually involved or whether both 'halves' of the molecule are derived from the lactam ester **35**. Consequently, the Diels-Alder adduct **39** of 2-methylfuran and acrylonitrile was prepared (figure 54), and this upon treatment with the lactam ester **35** under conditions similar to those above yielded a mixture of substituted 3-tolyl-6-phenyl-DPP **41** (figure 56) as a mixture (presumably the *m*- and *p*-tolyl isomers).

Figure 56:



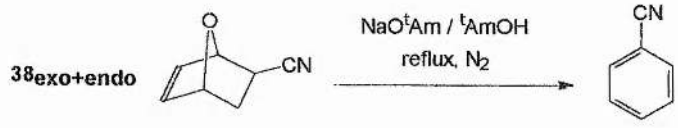
Furthermore, the reaction of 7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile **38** with diethyl succinate under conditions similar to the above also afforded 3,6-diphenyl-DPP **2** (figure 57). No unreacted nitrile **38** was recovered, but rather benzonitrile, as confirmed by ^{1}H NMR and GC analysis.

Figure 57: Novel synthesis of diphenyl-DPP



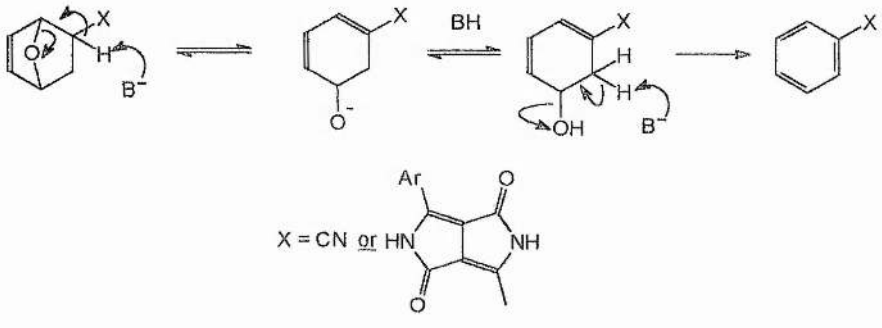
To test the stability of the nitrile **38** under similar conditions, it was heated to reflux in sodium *t*-amyloxide (figure 58) alone without the lactam ester reagent. The reaction yielded benzonitrile and unreacted nitrile **38**, but not with quantitative recovery.

Figure 58: Control experiment



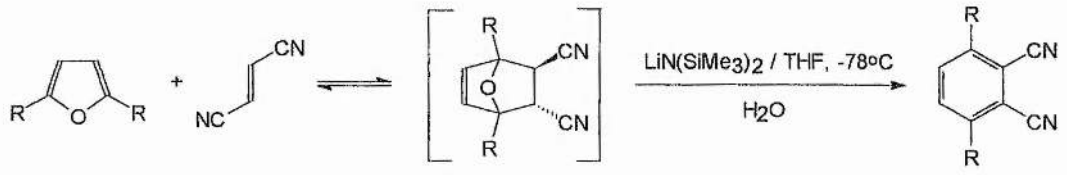
In the original reaction of nitrile **38** with the lactam ester **35** (figure 55) one can therefore conclude that the source of one phenyl ring in the 3,6-diphenyl-DPP **2** is indeed the nitrile reagent **38**. It is likely that the mechanism of the reaction entails ring opening followed by an elimination of the oxygen-bridging group of the nitrile in the presence of strong base (figure 59). On the basis of the present evidence one cannot conclude whether this elimination occurs before or after reaction of the nitrile moiety of reagent **38** with the lactam ester **35**. Nonetheless, these results have highlighted an efficient route for the preparation of functionalised benzonitrile derivatives for use in the synthesis of DPP derivatives, which may otherwise be difficult to obtain. This chemistry may also be optimised to provide a one-pot synthesis of DPP derivatives.

Figure 59: Proposed mechanism



The importance and versatility of the Diels-Alder reaction in the construction of six-membered rings is long established. Literature investigation confirmed that the base-catalysed elimination mechanism proposed above for the adducts of furans, although less common than the acid-catalysed mechanism, is not novel: for example it has been put to synthetic use in the preparation of phthalonitriles (figure 60).[72]

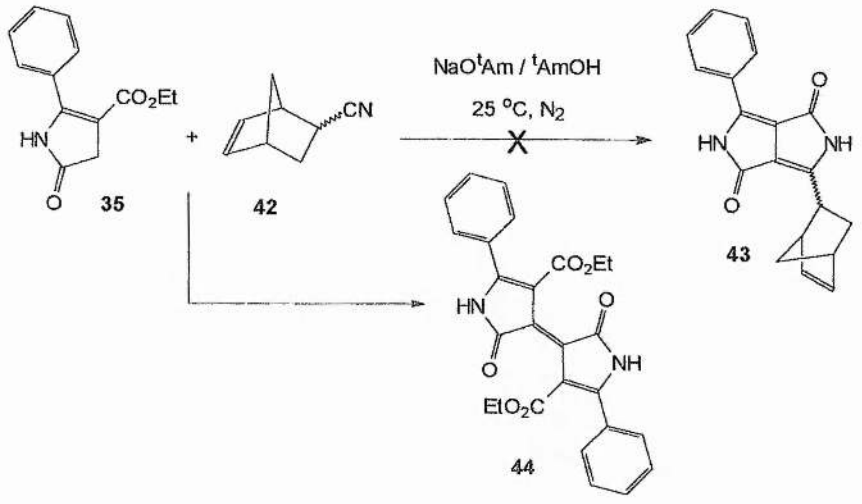
Figure 60



2.4.2 Cyclopentadiene-derived nitriles

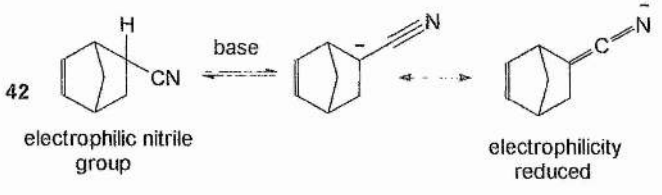
The results have established that nitriles prepared from the Diels-Alder reactions of furan cannot be used as reagents to synthesise alkenyl-DPPs precursors **28**. Consequently, reaction of the lactam ester **35** with another Diels-Alder adduct incorporating a nitrile functionality was investigated. The Diels-Alder reaction of cyclopentadiene with acrylonitrile is documented[73] and under flash vacuum pyrolysis conditions at 350-380 °C, this adduct was reported[73] to undergo retro Diels-Alder reaction. When a commercial sample of 5-norbornene-2-carbonitrile **42** was reacted with the lactam ester **35** in sodium *t*-amyloxide (figure 61), the reaction temperature was maintained at 25 °C during several days to prevent this retro Diels-Alder side-reaction of the nitrile reagent. However, none of the desired product **43** was obtained and instead, only unreacted starting materials were recovered in addition to a purple solid, characterised by ^{1}H NMR as the indigoid-type material **44**. This purple material was presumed to have been formed from oxidative dimerisation of the lactam ester reagent **35**.

Figure 61:



Some nitrile **42** was also recovered unchanged from the above reaction, although not in quantitative yield. Clearly, any retro Diels-Alder reaction that may have occurred did not deplete all of the nitrile reagent. This cannot, therefore, be offered as an explanation for the failure of the reaction. Instead only a hypothesis can be proposed at this stage. The failure to react could be attributed to the relative acidity of the α-hydrogen in **42**. Upon exposure to sodium *t*-amyloxide, any deprotonation at the α-position (figure 62) in **42** would have greatly reduced the electrophilicity of the nitrile functionality, so preventing nucleophilic attack by the anion of the lactam ester **35**. Alternatively, or additionally, the bicyclic moiety of nitrile **42** could have sterically hindered an attack by the bulky lactam ester nucleophile at the cyano-carbon.

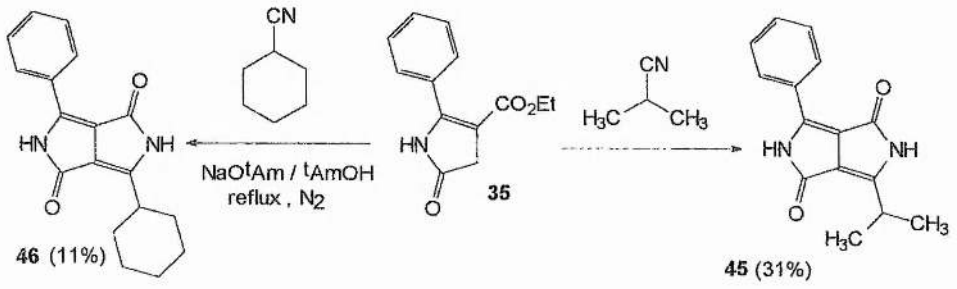
Figure 62



2.4.3 Secondary alkyl nitriles

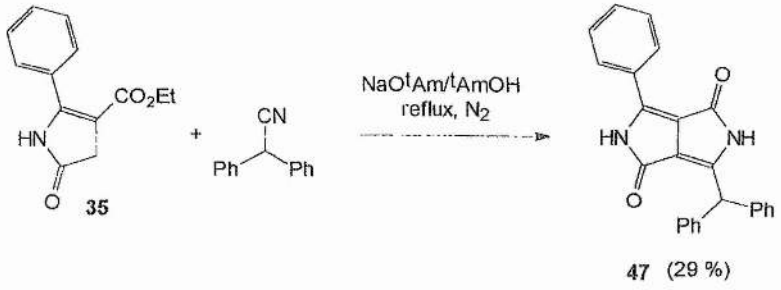
To investigate whether this hypothesis was correct, experimental evidence was sought. To substantiate the acidity arguments, the reaction of the lactam ester **35** with a number of secondary alkyl nitriles was investigated. Furthermore, a degree of steric hindrance was incorporated into some of these nitriles so that the importance of steric hindrance in the reaction could be probed. In the first instance, both isobutyronitrile and cyclohexanecarbonitrile were tested in the standard DPP synthesis. Upon reaction with the lactam ester **35** in sodium *t*-amyloxide, isobutyronitrile yielded an insoluble, yellow material which was characterised as 3-isopropyl-6-phenyl-DPP **45**. Similarly, cyclohexanecarbonitrile underwent reaction with the lactam ester **35** to yield the yellow 3-cyclohexyl-6-phenyl-DPP **46**. Both these materials were novel DPP pigments (figure 63), affording a yellow shade in the solid state, a colour previously difficult to achieve in the DPP series.

Figure 63



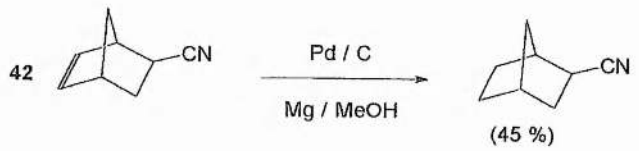
In addition, the more sterically hindered and more acidic diphenylacetonitrile underwent reaction with the lactam ester **35** in sodium *t*-amyloxide to afford the novel DPP **47** (figure 64). Similarly, this was a yellow solid, insoluble in common organic solvents. These three novel derivatives were characterised by ^{1}H NMR and elemental analysis.

Figure 64



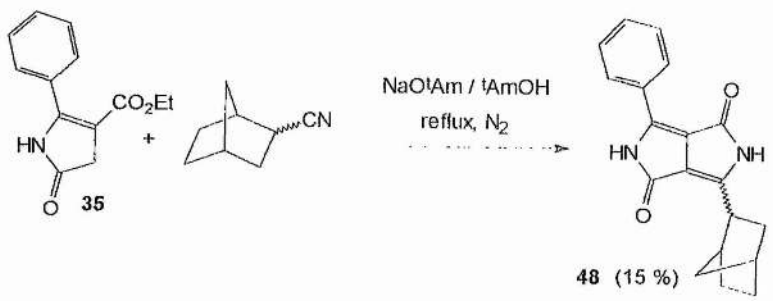
These results provide evidence to contradict the initial hypothesis that α-hydrogen deprotonation accounts for the failure of 5-norbornene-2-carbonitrile **42** to react. To investigate further the influence of steric factors, the saturated analogue of compound **42** was prepared via palladium-catalysed transfer hydrogenation of the unsaturated nitrile **42** (figure 65) according to a literature procedure.[74]

Figure 65: Hydrogenation of norbornenecarbonitrile



Upon reaction with the lactam ester **35** in sodium *t*-amyloxide, this nitrile yielded the novel DPP **48** (figure 66), although the reaction yield was low. The product was highly coloured (yellow) with low solubility in common organic solvents other than DMSO or DMF. A sample of sufficient purity for correct elemental analysis was not readily prepared; it was apparent from the ^{1}H NMR that there was a trace impurity since small ethyl ester resonances (δ_H 1.06 and 3.98) were observed - presumed to be unreacted ester **35**. The DPP product **48** is very similar to the desired precursors to alkenyl-DPPs, differing by only one carbon-carbon double bond. This result has not only provided an interesting DPP derivative, but offers evidence to negate the initial hypothesis that steric hindrance accounts for the failure of nitrile **42** to react. The DPP products **45-48** were submitted to Ciba Speciality Chemicals for testing of their performance as pigments. In every case various shades of yellow were observed upon inclusion of the samples into laquers. However, upon grafting into a PVC film, these products all showed too high a degree of migration, rendering them unsuitable for direct use as pigments.

Figure 66: Synthesis of a norbornyl-DPP



The reactions described above have provided important experimental evidence. The steric hindrance apparent in 5-norbornane-2-carbonitrile **42** suggests that the failure of nitrile **42** to react is not due to steric factors – at least not entirely. The successful reactions of isobutyronitrile, cyclohexanecarbonitrile and diphenylacetonitrile also indicate that deprotonation of the α-hydrogen of **42** is not the predominating factor. Only if nitrile **42** were even more acidic than the nitriles in this series could deprotonation have hindered the reaction significantly. A satisfactory explanation for the observed failure of **42** to react with the lactam ester **35** is therefore still required.

2.4.4 A cyclohexene-derived alkenyl-DPP precursor

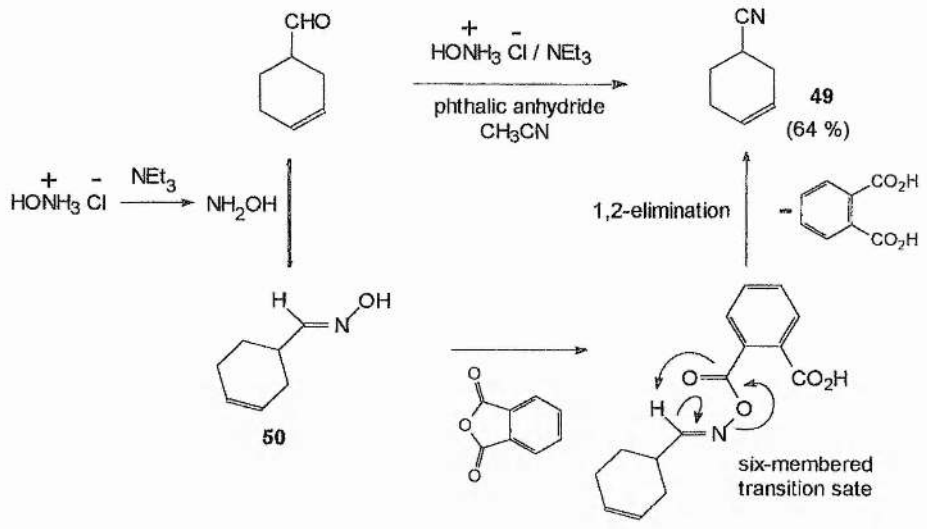
Since the nitriles derived from the Diels-Alder reaction of both cyclopentadiene and furan failed to undergo the desired reactions with the lactam ester **35**, an alternative approach to the alkenyl-DPP precursors **28** was sought. Secondary alkyl nitriles having been shown to react successfully with the lactam ester to yield DPPs, it was logical to build upon this success. Therefore, the cyclohexenyl moiety was considered as a potential precursor to an alkene functionality (figure 67). The retro Diels-Alder reaction has recently been reviewed in the context of flash vacuum pyrolysis.[75] In the literature, cyclohexene and substituted analogues are reported[76-81] to require higher temperatures to undergo retro Diels-Alder reaction than bridged bicyclic ring systems (e.g. norbornene[73] or oxabicyclo[2.2.1]heptene). This is attributed to the fact that no ring strain is relieved in the reaction and so the energy required is higher.

Figure 67:

To prepare a DPP with a cyclohexenyl moiety, a suitable nitrile was first required. Literature investigation revealed a recent method for the conversion of aldehydes to nitriles by dehydration of an oxime intermediate with phthalic anhydride.[82] The procedure was adapted to prepare cyclohex-3-ene-1-carbonitrile **49** from 1,2,4,6-tetrahydrobenzaldehyde in a one-pot reaction (figure 68). This straightforward

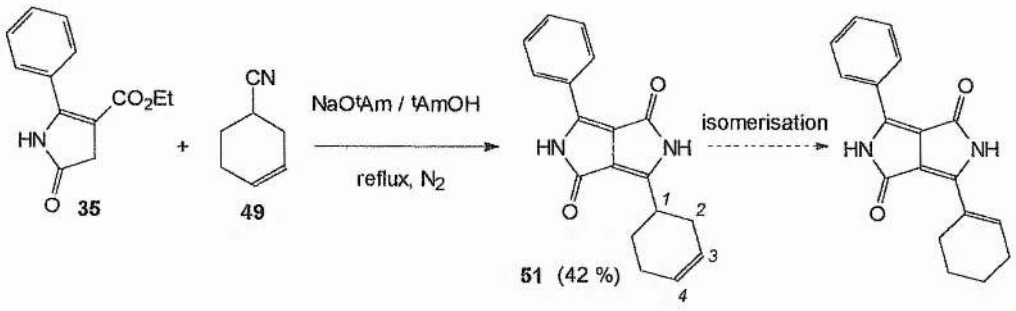
reaction circumvented the use of butadiene gas in the laboratory. The mechanism proposed[82] entails: (1) release of hydroxylamine from its hydrochloride salt by triethylamine, (2) its reaction with the aldehyde to form the oxime **50**, (3) subsequent ring opening of phthalic anhydride via nucleophilic attack of the hydroxy group of the oxime, and (4) finally intramolecular 1,2-elimination via a six-membered transition state (figure 68).

Figure 68



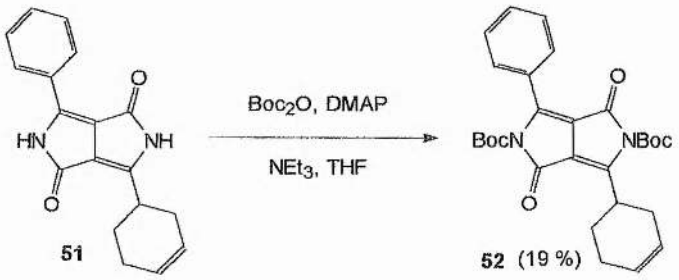
This nitrile underwent reaction with the lactam ester **35** in sodium *t*-amyloxide to yield a yellow, insoluble material (figure 69). Initial characterisation via mass spectral, NMR and elemental analysis was consistent with the expected structure **51**, but the position of the isolated carbon-carbon double bond in the cyclohexenyl moiety was uncertain. In the strongly basic reaction medium, it was considered possible that isomerisation of this double bond might have occurred, initiated by deprotonation at position C1 of the cyclohexenyl moiety. However, the isomerisation of cyclohex-3-ene-1-carbonitrile to cyclohex-1-ene-1-carbonitrile is reported in the literature to proceed in the gas phase and requires high temperature (250-350 °C) and either a dehydrating agent[83-84] (e.g alumina) or iron pentacarbonyl[85] catalysis. Under the relatively mild conditions of the DPP synthesis above, it would therefore be surprising to observe any isomerisation of the double bond. Nonetheless, to complete the characterisation and provide conclusive evidence for the double bond position before proceeding further, the derivatisation of the material was completed. The aim was to grow single crystals suitable for X-ray diffraction studies.

Figure 69: Synthesis of 3-(cyclohex-3-enyl)-6-phenyl-DPP



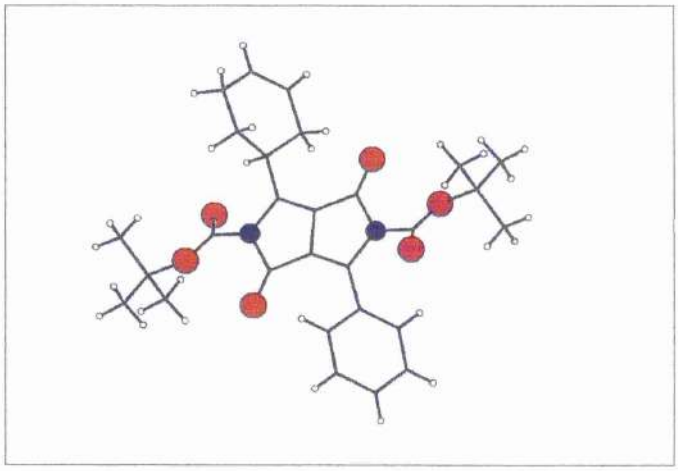
N-Boc protection of the product was readily effected via reaction with di-*t*-butyl dicarbonate in tetrahydrofuran, and DMAP catalysis with a stoichiometric amount of triethylamine, although the product was obtained in low yield. The protected product **52** was a bright yellow fluorescent material, readily soluble in common organic solvents. Recrystallisation from ethanol-tetrahydrofuran yielded single crystals suitable for X-ray analysis.

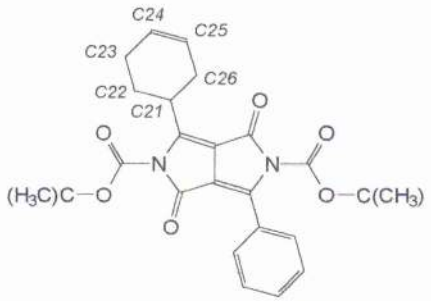
Figure 70: Boc protection of 3-(cyclohex-3-enyl)-6-phenyl-DPP



The crystal structure was complicated by a high degree of disorder, caused both by the Boc groups and by randomisation of the phenyl and cyclohexenyl moieties. The structural refinement (figure 71), however, was achieved by Prof. George Ferguson (University of Guelph, Ontario, Canada). The selected data shown in figure 71 shows that the critical C24-C25 bond is short, consistent with a double bond and that the C23-C24-C25 and C24-C25-C26 bond angles are greater than 120 °C, consistent with geometry about a carbon-carbon double bond. The refinement of the double bond to the 3-position as expected was unambiguous, thus completing characterisation.

Figure 71: X-ray structure (full details available in Appendix 1, page 145)





atom numbering consistent with diagram in Appendix 1

atoms	bond distance (Å)
C24 - C25	1.348(14)

atoms	bond angle (°)
C23 - C24 - C25	123.3(8)
C24 - C25 - C26	122.2(7)

3-(Cyclohex-3-enyl)-6-phenyl-DPP **51** is a direct precursor to a conjugated alkenyl-DPP and is an alkenyl-DPP in its own right. In fact, this DPP derivative is believed to be the first example of a DPP derivative containing an isolated carbon-carbon double bond.

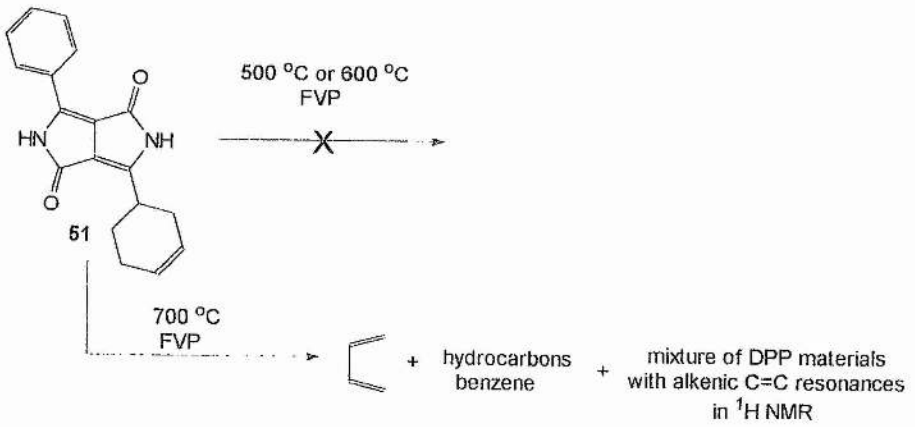
Pyrolysis studies were undertaken on this cyclohexenyl-DPP to examine whether the target alkenyl-DPP could be generated via a retro Diels-Alder reaction. In order to test the procedure, the original 3,6-diphenyl-DPP **2** was subjected to flash vacuum pyrolysis (FVP) conditions at 700 °C. Starting material was recovered as confirmed by infra-red analysis, thus confirming that the central DPP heterocycle was stable to such high temperature conditions. 3-(Cyclohex-3-enyl)-6-phenyl-DPP **51** was then subjected to FVP at 500 °C; unreacted starting material was recovered without

evidence of decomposition. Increasing the temperature to 600 °C had no effect with starting material again recovered unchanged. When the temperature was increased to 700 °C, decomposition did occur to yield 1,3-butadiene, identified by comparison of its ^{1}H NMR with the published spectrum.[87] Traces of benzene were collected in the trap, and were identified similarly from the NMR spectrum, which also indicated the presence of other unidentified hydrocarbons.

A fluorescent orange solid was collected at the furnace outlet and examined by ^{1}H NMR (the solid was sufficiently soluble in DMSO for this analysis). This showed that the cyclohexene ring had been broken (the ring methylene resonances had disappeared) and that there were resonances in the 5.8-6.8 ppm region of the spectrum consistent with an alkenic carbon-carbon double bond. However, the integral of these signals was too small relative to those in the aromatic region to correspond to a single compound. The data were consistent with a mixture of DPP materials, and it was assumed that the central DPP moiety had survived the high temperature on the basis of the evidence from the experiment conducted on diphenyl-DPP above. At these high temperatures, a free-radical source may be generated which is sufficient to effect free radical polymerisation of any alkenyl-DPP. The literature indeed offers precedent for this; styrene itself sets to a hard, glass-like material (polystyrene) from similar polymerisation initiated by a light source.[87]

These results are therefore not fully conclusive, but do demonstrate that a retro Diels-Alder process has occurred to release butadiene. However, further work would be required to develop this chemistry.

Figure 72: Entry to conjugated alkenyl-DPP



2.5 Attempted *N*-protection of the lactam ester 35

In order to remove the acidic amide proton of the lactam ester reagent and so prevent deprotonation at this position during the DPP synthesis, the *N*-Boc substitution of this reagent was attempted. The reaction of the lactam ester **35** with di-*t*-butyl dicarbonate in tetrahydrofuran with DMAP catalyst did not give the desired *N*-substituted product **53** but rather yielded the pyrrole **54** (figure 73), as confirmed by single crystal X-ray analysis (figure 74). This is an interesting route to unusual pyrrole derivatives, but did not provide the desired lactam ester derivative for further studies. The *O*-acylated product **54** obtained contains an aromatic pyrrole ring whereas the desired *N*-Boc protected lactam ester **53** does not. The stability associated with the formation of an aromatic system is a driving force that may explain the outcome of the reaction.

Figure 73: Route to pyrroles

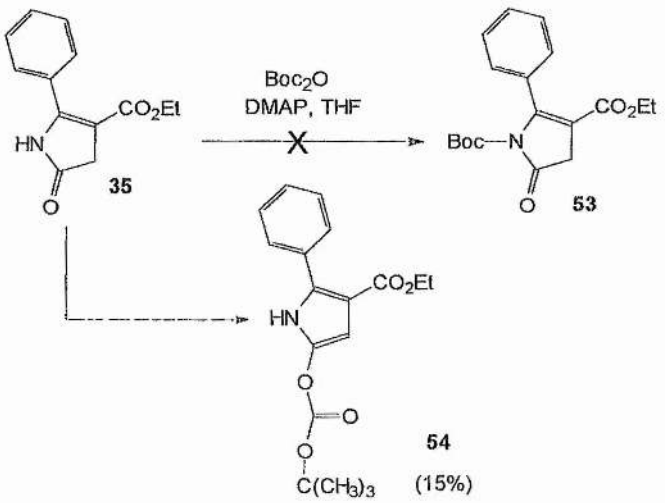
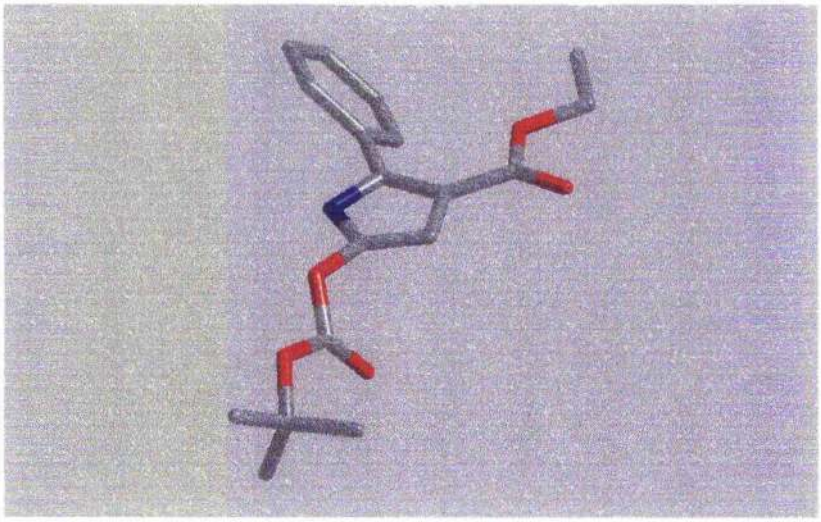


Figure 74: X-ray (full details available in Appendix 2 - page 150)



2.6 Conclusions

The synthetic efforts described above have shown that the Diels-Alder adducts derived from acrylonitrile and cyclopentadiene and furan do not provide the desired alkenyl-DPP precursors **28** upon reaction with the lactam ester **35**. The similar reaction of secondary alkyl nitriles did, however, afford a series of DPP derivatives and also offered important evidence to explain the failure of norbornenecarbonitrile to react with the lactam ester. Most importantly, it was possible to prepare the alkenyl-DPP precursor **51** from cyclohex-3-ene-1-carbonitrile, which showed potential for the future development of alkenyl-DPPs.

Chapter 3

ALTERNATIVE APPROACHES TO ALKENYL-DPP PRECURSORS

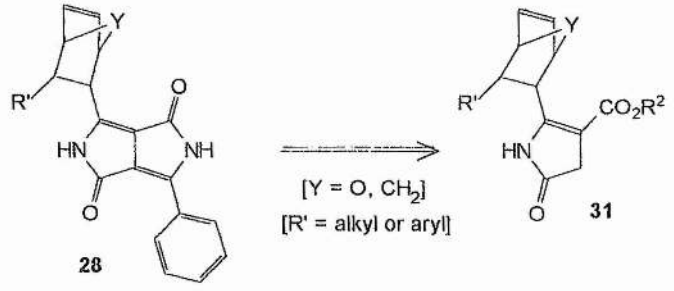
3.1 Introduction

Synthetic efforts towards alkenyl-DPP precursors **28**, entailing the reaction of a bicyclic nitrile (prepared via a Diels-Alder reaction) with the lactam ester **35** have been described in Chapter 2. An alternative approach towards the synthesis of these precursors and the separate synthesis of furyl-DPPs are discussed below.

3.2 Attempted synthesis of a new lactam ester intermediate

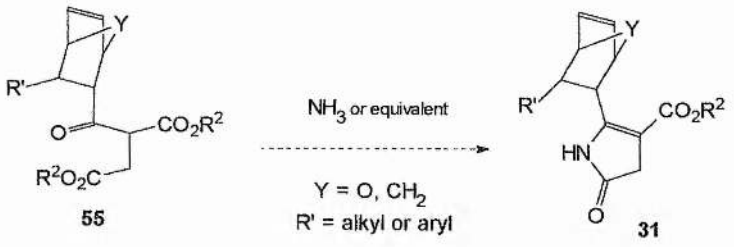
Disconnection of the desired alkenyl-DPP precursors **28** indicates a potential synthesis from a lactam ester **31** incorporating the necessary bicyclic moiety (figure 75).

Figure 75



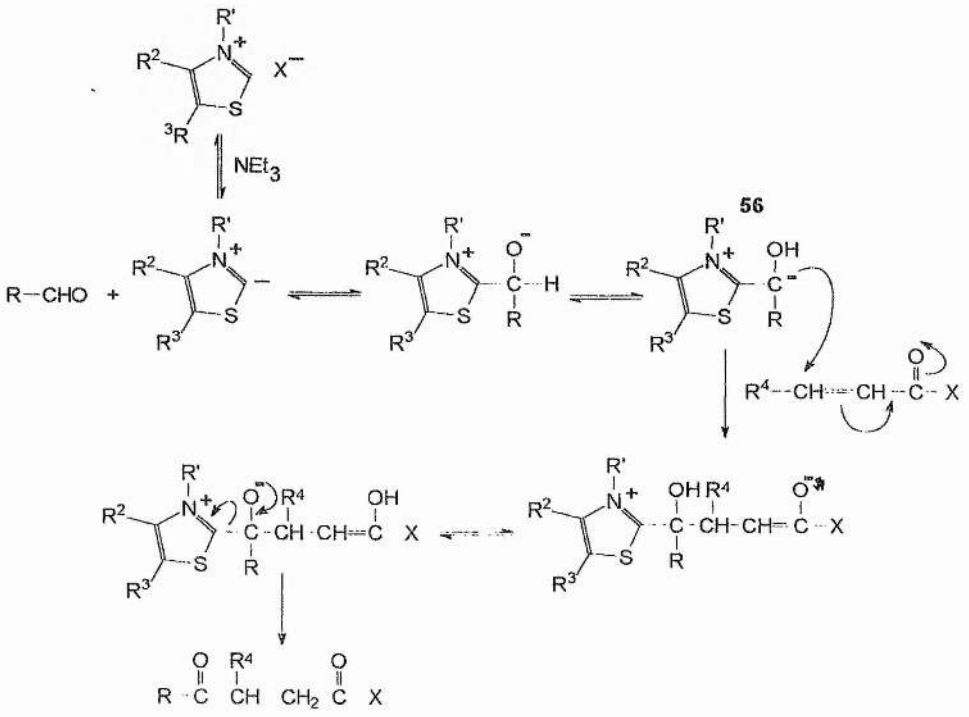
It was envisaged that such lactam esters could be prepared from an acylsuccinate **55**, which may undergo cyclisation upon treatment with an ammonia equivalent (figure 76). Therefore, initial synthetic efforts were directed towards the preparation of such compounds and in particular, the addition of diethyl maleate to a suitable aldehyde.

Figure 76



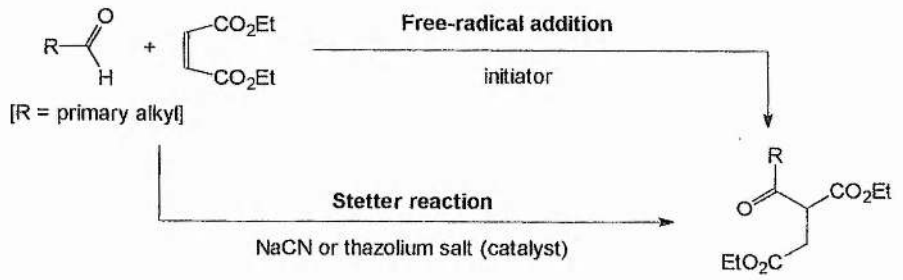
The addition of diethyl maleate to 5-norbornene-2-carboxaldehyde was first examined and two main approaches to this reaction were tested. Firstly, the addition of aldehydes to activated double bonds catalysed by a thiazolium salt is well documented and amounts to a nucleophilic acylation reaction (mechanism shown in figure 77). This is a modification of the classical Stetter reaction[88-89] in which cyanide is used as the catalyst. The addition of 5-norbornene-2-carbonitrile to alkyl acrylates has been reported by Stetter *et. al*[90-91] and more recently by Ponticello *et. al.*[92] However, the electron-withdrawing ester groups are reported to deactivate the carbon-carbon double bond of diethyl maleate towards addition and, indeed, these reactions are reported to be less favourable than the catalysed addition of aldehydes to α,β-unsaturated ketones. Nonetheless, this literature precedent offered potential for the successful development of a similar reaction with diethyl maleate.

Figure 77: Stetter reaction catalysed by a thiazolium salt



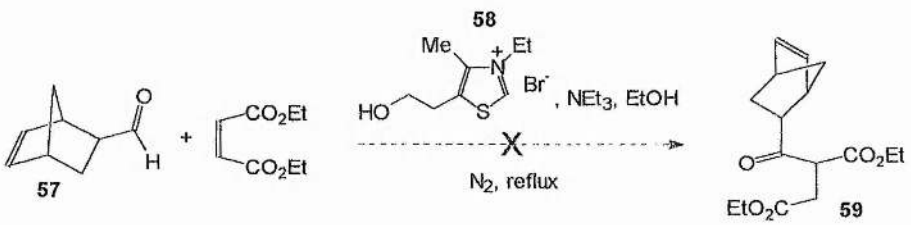
Secondly, the free radical addition of aldehydes to unsaturated polycarboxylic acid esters is reported in the literature[93-96] and has been demonstrated in the case of diethyl maleate addition to certain aldehydes (figure 78).

Figure 78: Literature methods for acylation of diethyl maleate



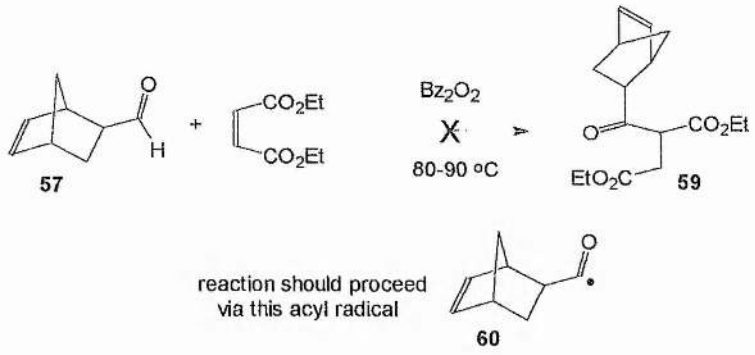
Upon treatment of diethyl maleate with 5-norbornene-2-carboxaldehyde **57** in the presence of the thiazolium salt **58** (figure 79), no addition product **59** was observed and only unreacted starting materials were recovered. The reaction was repeated in the polar, aprotic solvent DMF to enhance the reactivity of the nucleophilic species, but this had no effect and starting materials were again recovered unchanged as confirmed by ^{1}H NMR.

Figure 79: Attempted acylation via a Stetter reaction



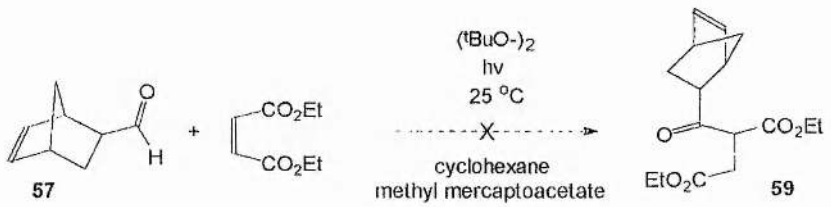
To examine the free-radical addition, the reaction of diethyl maleate with **57** using dibenzoyl peroxide as a free-radical initiator (figure 80) was completed at 80-90 °C. The reaction temperature was maintained carefully below 100 °C to prevent appreciable decarbonylation of the acyl radical **60**. The reaction yielded none of the addition product **59** and only starting materials were recovered.

Figure 80: Attempted acylation via free-radical addition



However, it is reported in the recent literature that thiols catalyse the free-radical additon of aldehydes to double bonds by acting as a polarity-reversal catalyst that promotes the overall hydrogen-atom transfer from the aldehyde to the carbon-centred radical produced by addition of the acyl radical (such as **60**) to the alkene.[97] The reaction of **57** with diethyl maleate was repeated, but this time di-*t*-butyl peroxide was employed as initiator (the temperature was lowered to 25 °C and the radical source then generated using an ultra-violet light source) and methyl mercaptoacetate was used as the catalyst (figure 81). This had the dual benefit of introducing a catalyst to the process and of lowering the reaction temperature so that any possible retro Diels-Alder reaction of the reagent **57** could be prevented. However, the reaction did not proceed to the desired addition product **59**, with only unreacted starting materials recovered.

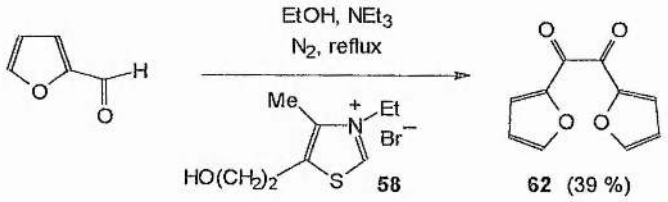
Figure 81



However, in the course of studies into the Stetter reaction, the reaction of diethyl maleate with furfural in ethanol was tested under thiazolium salt catalysis. The reaction proceeded to give the expected addition product **61** in low yield (figure 83). When the reaction was repeated in DMF, the yield was greatly increased, presumably due to the increased reactivity of the anionic furfural-derived species (similar to **56** in figure 77 - page 55) formed during the reaction. The conditions were optimised to

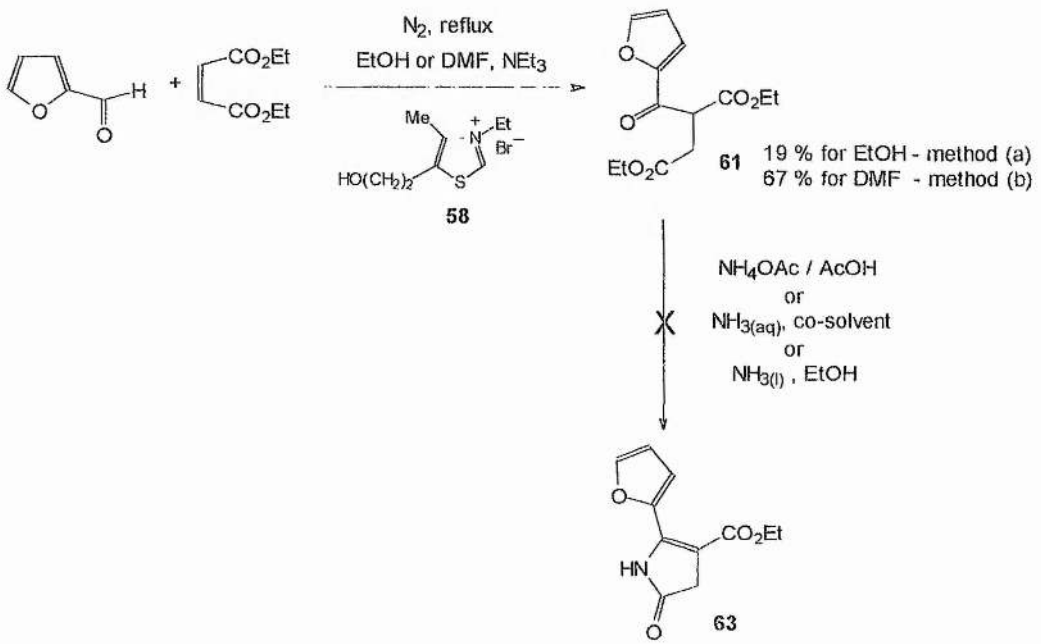
prevent formation of furil **62** from the oxidation of furoin: a reaction which is also catalysed by the thiazolium salt.[99] For this purpose, the reaction was repeated without the addition of diethyl maleate (figure 82) so that an authentic sample of furil **62** could be prepared to confirm that no such side reaction had occurred in the original reaction.

Figure 82



Under various conditions the reaction of the addition product **61** with an ammonia equivalent (described in figure 83) did not afford the cyclised lactam ester product **63** but rather a black intractable solid or unreacted starting material as confirmed by ^{1}H NMR; it was presumed that polymerisation of the furan moiety had occurred.

Figure 83: Attempted synthesis of a furyl lactam ester

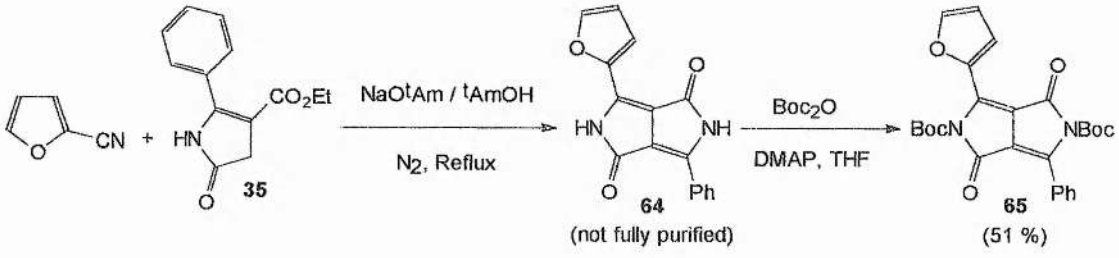


3.3 Furyl-DPPs

3.3.1 Synthesis of furyl-DPPs

In Chapter 1 (section 1.5.3 - page 34) the idea was introduced of preparing furyl-DPPs with the intention of providing monomers for Diels-Alder polymerisation, which may also be amenable to further interesting chemistry. The preparation of 2-furyl DPPs was completed. The reaction of the lactam ester **35** with 2-furonitrile in sodium *t*-amyloxide yielded a red-purple solid, characterised as the 2-(2-furyl)-6-phenyl-DPP **64** (figure 84). The *N*-Boc substitution of this pigment was completed by reaction with di-*t*-butyl dicarbonate in tetrahydrofuran, employing DMAP as catalyst.

Figure 84



Moreover, the the reaction of pigment **64** with methyl tosylate in the presence of potassium carbonate in nitrobenzene yielded the *N*-methylated product **66** (figure 85). This was recrystallised to provide single crystals for X-ray (figure 86).

Figure 85

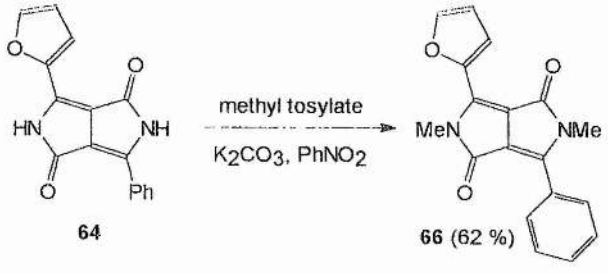
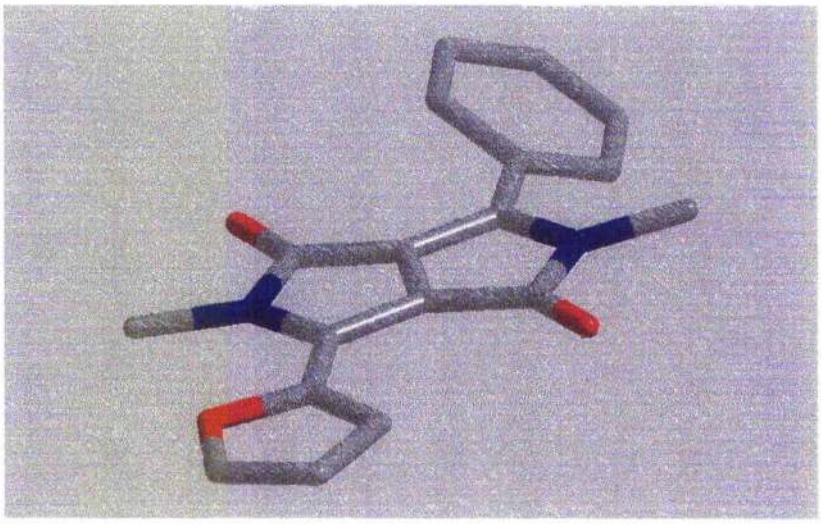
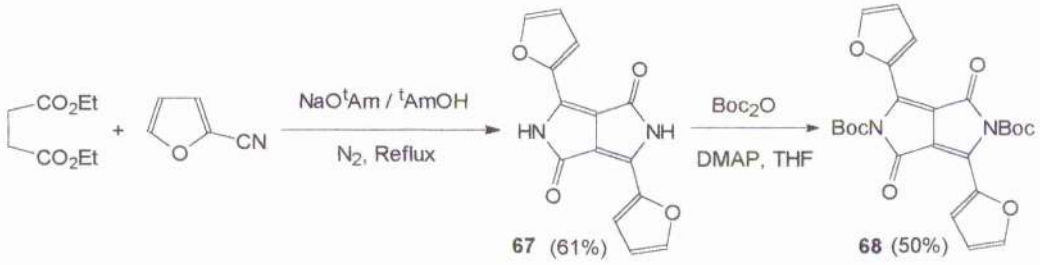


Figure 86: X-ray structure (full details available in Appendix 3 - page 156)



In addition, the reaction of diethyl succinate with 2-furonitrile in sodium *t*-amyloxide yielded the purple 3,6-di-(2-furyl)-DPP **67** (figure 87). This compound has been claimed in the patent literature[26], but full characterisation was not reported. *N*-Boc substitution was readily effected via reaction with di-*t*-butyl dicarbonate in tetrahydrofuran, employing DMAP as catalyst (figure 87).

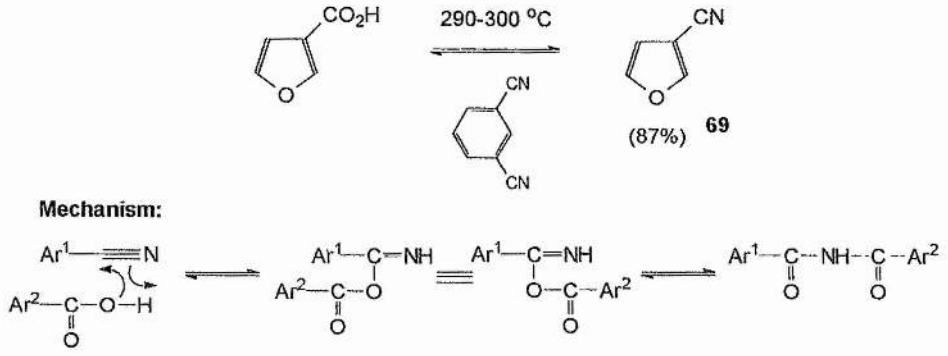
Figure 87



Further to the 2-furyl-DPPs reported above, 3-furyl DPPs were prepared so that the steric hindrance of the diene moiety could be reduced. The further possible utility of these DPPs was discussed in Chapter 1 (section 1.5.3 page 34). For this purpose, 3-furonitrile was first required. Srogl and co-workers[99] reported the synthesis of 3-furonitrile from 3-bromofuran and CuCN-KCN in quinoline. In addition, Toland et.al[100] reported a general method for the conversion of aromatic carboxylic acids into nitriles, which was demonstrated in the case of 3-furoic acid by Garst et. al.[101]

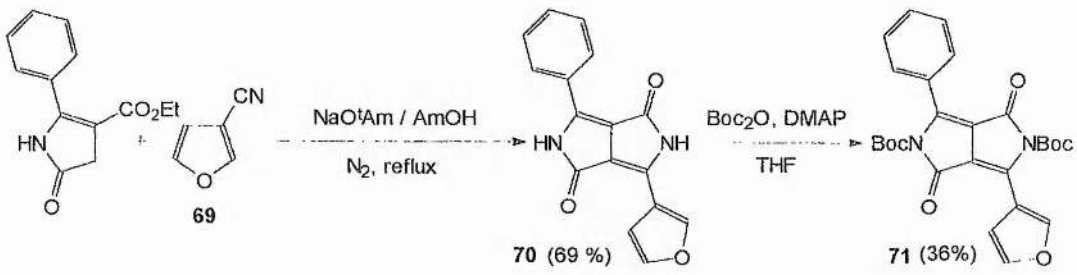
This latter method was used to prepare 3-furonitrile; 3-furoic acid was reacted with 1,3-dicyanobenzene to afford 3-furonitrile **69** in high yield (figure 88). The product was separated easily from the reaction mixture via fractional distillation. It is believed in the literature[100] that the mechanism for this reaction entails an exchange of the nitrile and carboxylic acid functionalities through a series of equilibria, via an isoimide intermediate.

Figure 88



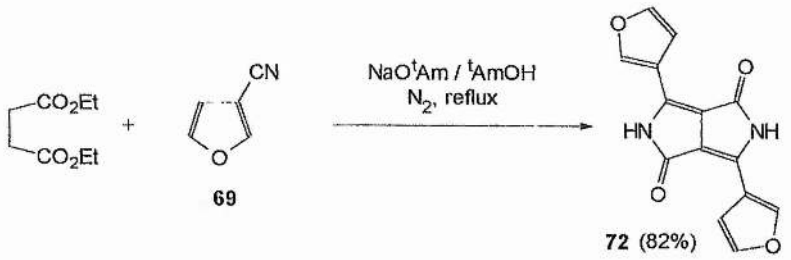
When nitrile **69** was reacted with the lactam ester **35** in sodium *t*-amyloxide a purple-red solid was isolated. Subsequent reaction of this solid with di-*t*-butyl dicarbonate in tetrahydrofuran, employing DMAP as catalyst (figure 89) provided the *N*-Boc protected product **71** which then allowed complete characterisation of the 3-(3-furyl)-6-phenyl-DPP product **70**.

Figure 89



Furthermore, the symmetrical 3,6-di(3-furyl)-DPP **72** was prepared from the reaction of diethyl succinate with nitrile **69** in sodium *t*-amyloxide, as confirmed by ^{1}H NMR. This material was not obtained completely pure, however, with low elemental analysis suggesting a trace amount of inorganic impurities from the work-up.

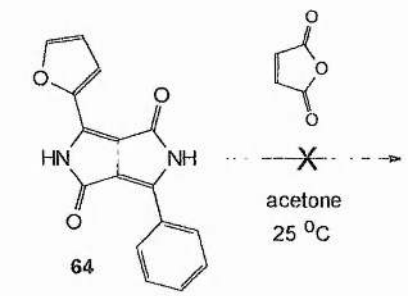
Figure 90



3.3.2 Diels-Alder reaction of furyl-DPPs

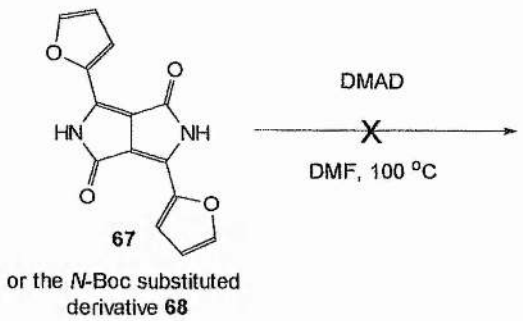
The reaction of the furyl-DPPs with various dienophiles was examined. 2-(2-Furyl)-6-phenyl-DPP **64** was reacted with maleic anhydride in acetone at 25 °C during several days, but only unreacted starting materials were recovered. When the *N*-Boc substituted DPP derivative was reacted with maleic anhydride in acetone, all the reagents were fully in solution, but only unreacted starting materials were recovered. Addition of zinc iodide as a Lewis acid catalyst had no effect other than to partially remove the Boc groups from the DPP reagent. ^{1}H NMR was used to identify the materials isolated after reaction.

Figure 91



3,6-Di-(2-furyl)-DPP **67** then its *N*-Boc substituted derivative **68** were reacted with dimethyl acetylenedicarboxylate (DMAD) in DMF with heating to 100 °C. In both cases, only unreacted starting materials were recovered.

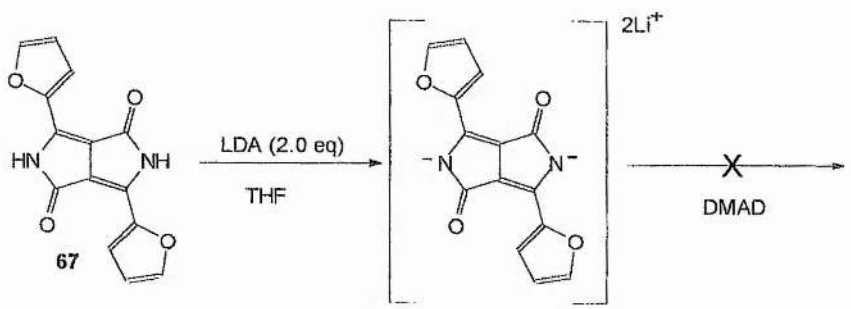
Figure 92



However, the 2-furyl-DPPs have sterically hindered diene moieties, and the DPP heterocycle itself functions as an electron-withdrawing substituent on the furyl diene, deactivating it towards Diels-Alder reaction. Both these factors could account for the failure of the above reactions.

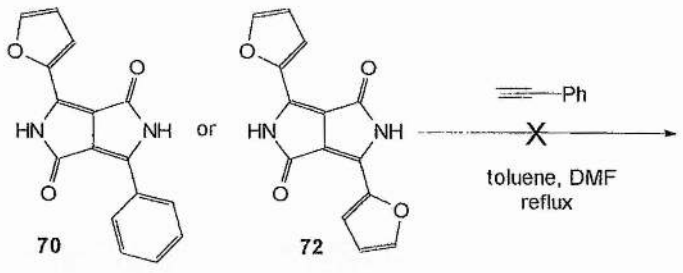
In an effort to reverse the electron withdrawing nature of the DPP heterocycle, the dianion of 3,6-di-(2-furyl)-DPP **67** was prepared by deprotonation with LDA in THF. This was then reacted with DMAD during several days, but only unreacted starting materials were recovered, as confirmed by ^{1}H NMR.

Figure 93



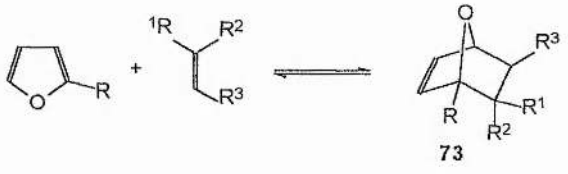
In the case of 3-furyl-DPPs, it was envisaged that the decrease in the steric hindrance of the diene moiety might enable Diels-Alder reaction to proceed with a suitable dienophile; phenylacetylene was selected as an electron-rich dienophile. When 3-(3-furyl)-6-phenyl-DPP **70** was reacted with phenylacetylene in a toluene / DMF mixture, no reaction was observed by ^{1}H NMR after several hours of heating to reflux. A similar result was observed when the reaction of 3,6-di(3-furyl)-DPP **72** with phenylacetylene was attempted under similar conditions. The DMF solvent allowed complete dissolution of the reagents and ^{1}H NMR confirmed that unreacted starting materials were recovered.

Figure 94



All synthetic efforts to bring about Diels-Alder reactions with furyl-DPPs were unsuccessful. Both steric and electronic factors have been put forward as explanations for this failure, and the introduction of Lewis acid catalysis did not prove useful. However, if one looks to the published literature,[102] it is apparent that the Diels-Alder reaction of furans is sometimes difficult due to their tendency for cycloreversion (due both to the ring strain in the cycloadduct **73** and the aromatic character of furan itself - figure 95).

Figure 95



It has been shown that high pressure significantly increases the yield of the Diels-Alder adduct **73** from furan.[103-104] Typically, pressures of 13-20 kbar are reported. Such high pressure facilities were not available for a practical examination of this chemistry in the case of the furyl-DPPs. A full evaluation of the potential of utilising high pressure in the Diels-Alder reactions of furyl-DPPs would require further work and the availability of the appropriate equipment.

Chapter 4

THE SYNTHESIS OF DPP ANALOGUES

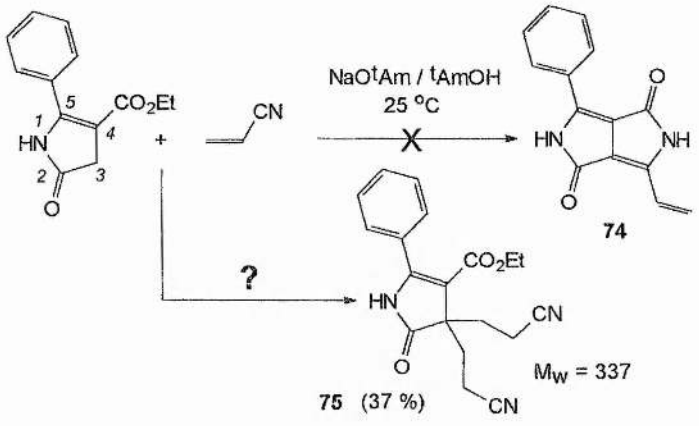
4.1 Introduction

Possible synthetic methods for preparing the precursors **28** to alkenyl-DPPs were introduced in Chapter 1 (section 1.5.2, page 32). A synthesis starting from a succinic ester was initially proposed (figure 41, page 33), but it was recognised that conjugate addition may occur in addition to, or in preference to, 1,2-addition to the nitrile functionality. For this reason, the concept of introducing the alkenic functionality via a retro Diels-Alder approach was first taken forward into the laboratory. The experimental efforts in this regard were described in Chapter 2 and the reactions of norbornene-carbonitrile and of nitriles derived from the Diels-Alder reaction of furans were discussed. Despite the Michael acceptor[105-106] properties of α,β-unsaturated nitriles, it was still considered important to test the reactions of these nitriles in the hope of directly preparing alkenyl-DPP products. A variety of such nitriles have been tested in reaction with the lactam ester **35** and some interesting results are presented in this chapter.

4.2 Acrylonitrile derivatives

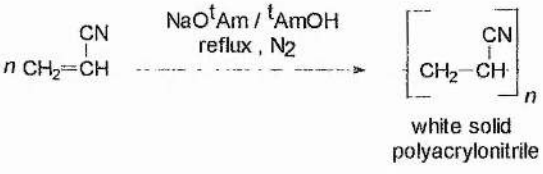
The reaction of acrylonitrile itself was first examined. This is a low molecular weight, highly volatile nitrile and to prevent appreciable loss of the reagent during reaction, the temperature was maintained below its boiling point (literature[107] 77 °C). Upon exposure of the lactam ester **35** to acrylonitrile in sodium *t*-amyloxide at 25 °C (figure 96), none of the desired product **74** was obtained. Instead, a beige coloured product was isolated and recrystallised, with no acrylonitrile recovered. The melting point and ^{1}H NMR spectrum confirmed that this product was not unreacted lactam ester **35**, indicating instead that substitution had occurred at position C-3 of the pyrrolinone ring. A nitrile functionality was still apparent from the infra-red spectrum and mass spectral data highlighted a molecular ion at m/z 337, suggesting that two moles of acrylonitrile had reacted per mole of **35**. It is proposed that conjugate addition of the anion of lactam ester **35** to acrylonitrile had occurred twice to give the product **75** shown in figure 96.

Figure 96



To examine the stability of acrylonitrile under the conditions above, the reaction of acrylonitrile in sodium *t*-amyloxide alone without the lactam ester **35** was attempted. At 25 °C, none of the acrylonitrile reagent was recovered, but rather a white, intractable solid product was isolated, assumed to be polyacrylonitrile, the product of anionic polymerisation[108] (figure 97). Acrylonitrile was apparently not stable to the original reaction conditions which at least partly explains why the reagent was not recovered from the reaction mixture.

Figure 97



It was decided to use a less volatile α,β-unsaturated nitrile and so the reaction of the lactam ester **35** with excess methacrylonitrile in sodium *t*-amyloxide was completed under the normal reflux conditions for DPP synthesis. The colourless product was readily recrystallised, allowing complete characterisation as compound **76** from single crystal X-ray analysis (figure 99). The reaction was observed to proceed via conjugate addition to the product **76**, with the reaction of two moles of methacrylonitrile for every mole of the lactam ester **35** (figure 98). When the reaction was repeated in tetrahydrofuran with sodium hydride as base, the same product **76** was obtained, but in higher yield and under milder conditions. It is apparent from the X-ray data that the geometry of the alkyl side chains about the

tetrahedral C-3 atom in this product could serve to prevent ring closure to a DPP heterocycle (i.e. the nucleophilic centre adjacent to the nitrile group cannot approach the ester carbonyl group). This result also supports the proposed structure for the product **75** above obtained from the corresponding reaction with acrylonitrile.

Figure 98

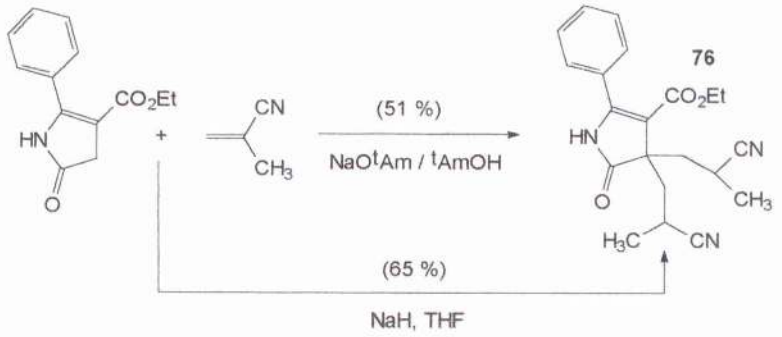
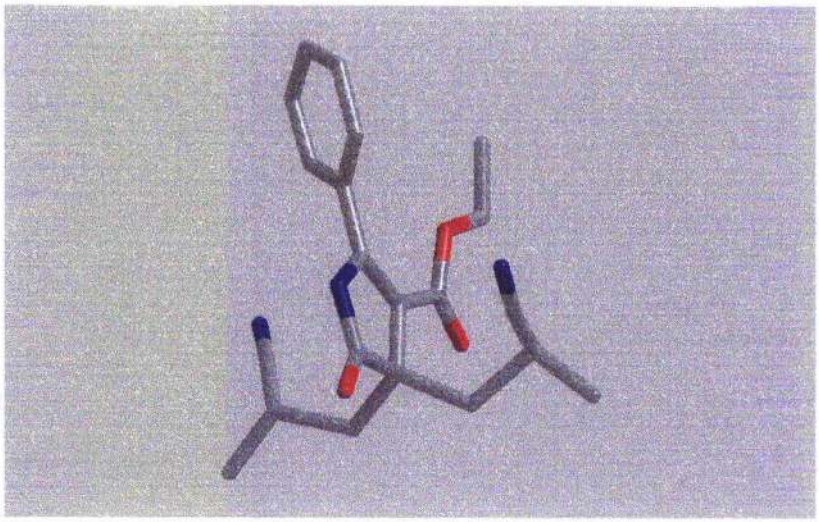


Figure 99: X-ray structure (full details available in Appendix 4 - page 163)

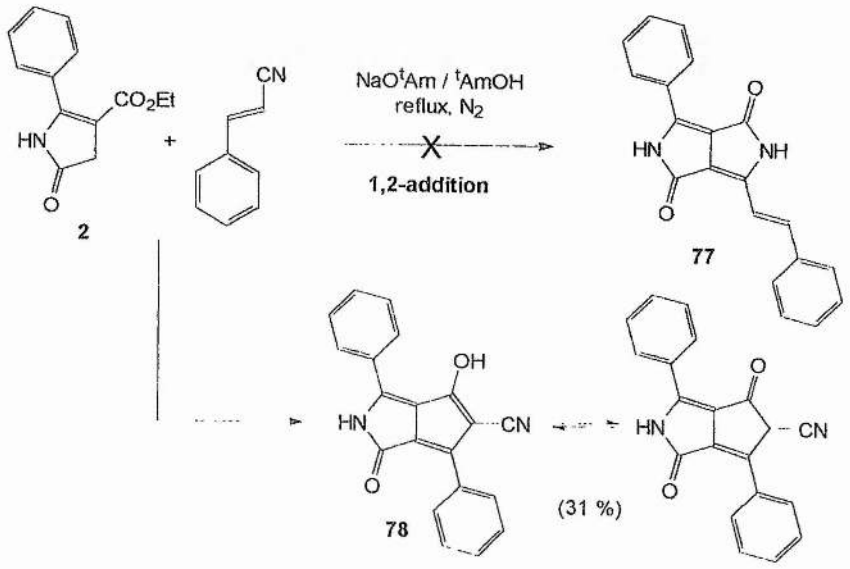


4.3 Analogues of DPP

4.3.1 Initial synthesis

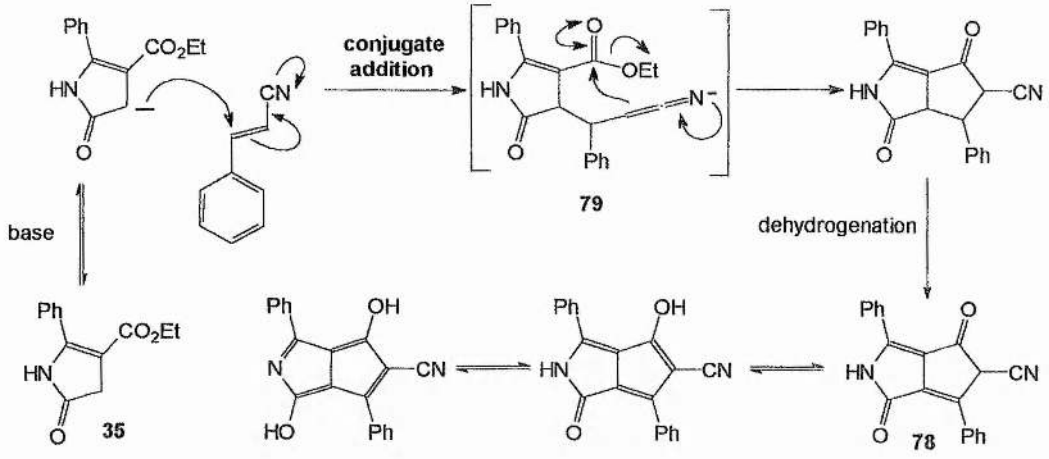
Further to the acrylonitrile and methacrylonitrile reactions discussed above, the similar reaction of cinnamonitrile was examined in order to extend the investigation to aryl α,β-unsaturated nitriles. The results obtained were both interesting and unexpected. Upon treatment of the lactam ester **35** with cinnamonitrile in sodium *t*-amyloxide (figure 100), a dark red solid was obtained after acid work up. The material was intensely coloured with high ε values, and was of very low solubility in common organic solvents, whilst only moderately soluble in DMSO or DMF. These physical properties were not dissimilar to those observed for DPP materials. Mass spectral data, ^{1}H NMR and infra-red analyses, however, suggested that this was not the desired alkenyl-DPP **77**, but rather a compound with a molecular mass 2 a.m.u. less. Infra-red analysis confirmed that both a nitrile and an amide functionality were present, but indicated the loss of the ester group from the starting lactam ester **35**. The infra-red spectrum showed a strong, but broad absorption at 3114 cm^{-1}, providing evidence for the N-H and O-H groups Together, the data substantiated the proposed structure **78**, 4-hydroxy-3,6-di-phenyl-2*H*-cyclopenta[*c*]pyrrol-1-one-5-carbonitrile, which could exist in both tautomeric forms. This synthesis has therefore led to the formation of a highly functionalised, bicyclic skeleton in a one-pot reaction from easily prepared, or commercially available, starting materials.

Figure 100



A hypothetical mechanism for the formation of product **78** is outlined below (figure 101). It is proposed that the reaction proceeds via conjugate addition of the lactam ester **35** to cinnamonitrile, producing a highly reactive ketimine intermediate **79** which could then cyclise to form the 5-membered carbocyclic ring. Subsequent dehydrogenation would lead to the aromatised product **78**, which might exist in one or more of several tautomeric forms.

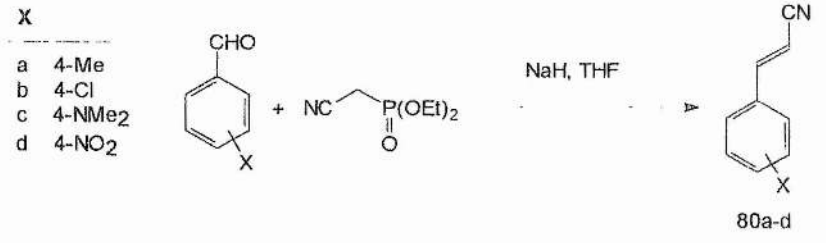
Figure 101: Proposed mechanism of formation



4.3.2 Generalisation of reaction to provide similar derivatives

In view of the intense colour of this material, several derivatives were immediately synthesised for an evaluation of their pigment properties and to probe whether this reaction could be generalised. A variety of substituted cinnamonitrile reagents **80a-d** were first prepared by adapting a conventional Horner-Wadsworth-Emmons[109], each consisting of a mixture of *E* and *Z* isomers (figure 102). In addition,4-methoxy-cinnamonitrile **80e** was obtained as a commercial sample.

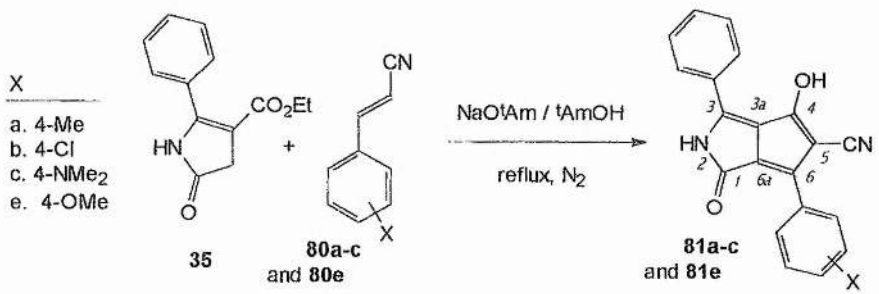
Figure 102



The lactam ester **35** underwent reaction in sodium *t*-amyloxide with 4-methylcinnamonitrile **80a**, 4-chlorocinnamonitrile **80b** and 4-dimethylamino-cinnamonitrile **80c** respectively to yield the substituted products **81a-c**. Similarly, 4-methoxycinnamonitrile **80e** afforded the derivative **81e**. In every case the data were similar with those observed for the product **78** obtained from cinnamonitrile itself (i.e. elemental analysis, ^{1}H and infra-red spectra). However, for the *p*-dimethyl-amino compound **81c**, a sample of sufficient purity for correct elemental analysis could not be prepared. A family of compounds was now available for examination. Each of these derivatives was intensely coloured and was of very low solubility in common organic solvents. The insolubility of these materials could perhaps be attributed to intermolecular hydrogen bonding which may exist between the amide carbonyl of one molecule and the amidic hydrogen of a neighbouring molecule.

However, 4-nitrocinnamonitrile **80d** did not undergo reaction with the lactam ester **35** in sodium *t*-amyloxide and instead only a brown intractable solid was obtained. It was presumed that the instability of the nitro group towards the strongly basic conditions accounted for this synthetic failure.

Figure 103



These materials were submitted to Ciba Speciality Chemicals for testing of their performance as pigments. The results showed that upon grafting into a PVC film, all of the products migrated, and more importantly the products were not sufficiently stable to light, with loss of colour upon minimum exposure time to sunlight. Both test results indicated that these compounds were not suitable for application as pigments directly. However, the intense colour of these materials and a requirement to complete their structural characterisation rendered a further investigation of their chemistry worthwhile.

4.3.3 Preliminary investigation of chemistry

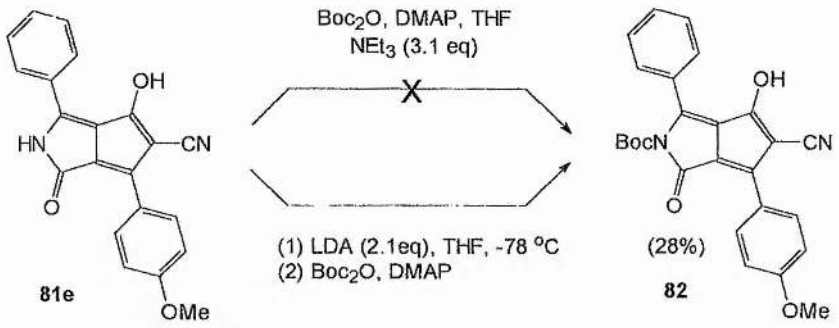
4.3.3.1 Introduction

A family of compounds has been prepared, the proposed cyclopenta[*c*]pyrrol-1-one structures being consistent with the data presented above. However, the characterisation of these novel materials was not fully conclusive since the bicyclic skeleton made elucidation of the NMR spectra more complex. Single crystal X-ray analysis was required to complete the characterisation. However, all these materials were of very poor solubility in common organic solvents and so normal recrystallisation techniques were not possible. Sublimation was then investigated in the hope of growing suitable single crystals from deposition in the gas phase, but this led instead to further reaction (see section 4.3.3.4 - page 76). Therefore, the syntheses of suitable derivatives with a much higher solubility were required so that recrystallisation could be accomplished. Moreover, the investigation of the chemistry of this new class of compounds would provide further insight into the potential suitability of these materials for development in application as pigments or as dyes.

4.3.3.2 *N*-Boc protection

The *N*-substitution of products **81** was investigated in an effort to solubilise these materials by removing the amidic hydrogen atom that is involved in intermolecular hydrogen bonding. The 4-methoxyphenyl derivative **81e** was chosen in order to simplify the subsequent NMR analysis. Treatment of this derivative with di-*t*-butyl dicarbonate in tetrahydrofuran with triethylamine and DMAP as catalyst yielded none of the desired *N*-substituted product. Instead, only unreacted starting material was recovered. It was observed, however, that a colour change to purple did result upon treatment of **81e** with lithium diisopropylamide (LDA). Consequently, the dianion of derivative **81e** was first generated by deprotonation with two equivalents of LDA before treatment with Boc_2O in the presence of DMAP catalyst to provide a purple solid in low yield, which was readily soluble in methanol. All spectral data was consistent with the structure **82** for the *N*-substituted product, but material of sufficient purity for correct elemental analysis could not be isolated and recrystallisation did not however provide crystals of sufficient quality for X-ray analysis.

Figure 104



4.3.3.3 Alkylation chemistry

In the review of literature methods presented in Chapter 1 (section 1.4.4 - page 20) the alkylation of diaryl-DPP materials was described. Normal methods to effect this transformation entail reaction with an alkyl halide or alkyl sulfonate in the presence of potassium carbonate. A suitable high boiling or dipolar aprotic solvent (such as nitrobenzene or DMF) at high temperature was used to ensure sufficient dissolution of the highly insoluble pigment during the reaction.

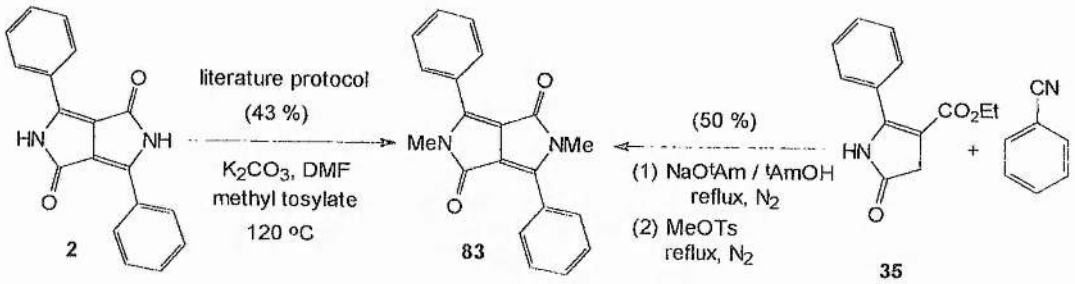
To examine the alkylation of the compounds **81** (figure 103), a variety of conditions were tested in the laboratory. Firstly, the reaction of the original compound **78** with methyl tosylate in nitrobenzene with potassium carbonate was attempted as described above for diaryl-DPPs, but gave only unreacted starting materials. Further conditions tested included the reaction with Meerwein salts in the presence of base as detailed in the table below.

base	solvent	temperature / °C	alkylating agent
potassium carbonate	nitrobenzene	200	methyl tosylate
none	tetrahydrofuran	25	$Et_3O^+BF_4^-$
sodium hydride	dichloromethane	25	$Me_3O^+BF_4^-$
sodium hydride	dichloromethane	25	$Et_3O^+BF_4^-$
lithium hexamethyldisilazide	tetrahydrofuran	25	$Et_3O^+BF_4^-$

None of the desired alkylation products were obtained from these reactions and instead only unreacted starting materials were recovered. Only when lithium hexamethyl disilazide was used as base was any colour change observed, indicative of the formation of an anion - a distinctive colour change to a dark purple colour did occur. Some evidence (namely ^{1}H NMR) was obtained to indicate that a degree of alkylation had occurred in this case, but attempts at purification were unsuccessful.

Instead, it was proposed that the anion of **78** could be intercepted directly in the original synthesis starting from the lactam ester **35**. To test this proposition, the synthesis of 2,5-dimethyl-3,6-diphenyl-DPP **83** was first completed from the reaction of diphenyl-DPP **2** with potassium carbonate and methyl tosylate in nitrobenzene according to literature protocol[55] to prepare a sample for spectral comparison (figure 105). The model synthesis of 3,6-diphenyl-DPP **2** was then repeated: the reaction of the lactam ester **35** with benzonitrile in sodium *t*-amyloxide was completed under reflux. However, rather than using an acid work up as before, the intermediate anion was quenched directly with a ten fold excess of methyl tosylate to yield the *N*-methylated product **83** in moderate overall yield (figure 105). This was an effective *in situ* alkylation procedure and removed the requirement to isolate and purify the parent DPP pigment **2**.

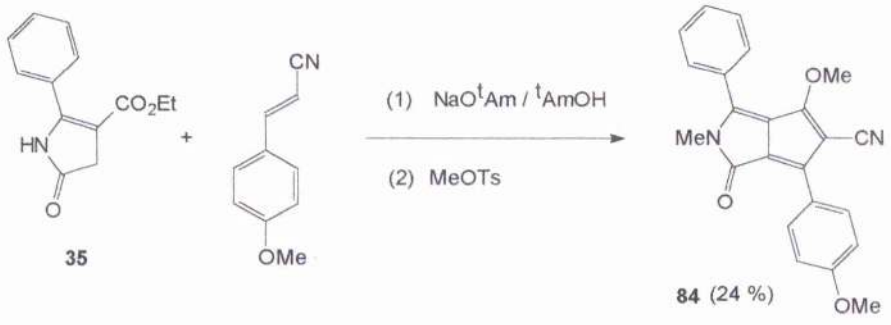
Figure 105

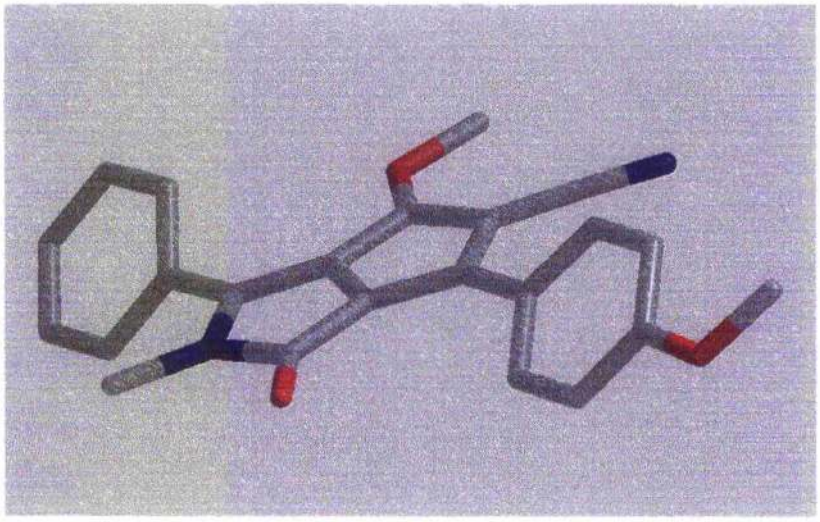


With this successful result in hand, the reaction of the lactam ester **35** with cinnamonitriles was repeated and *in situ* methylation was completed under similar conditions to afford a red-orange coloured derivative (figure 106). The *p*-methoxy compound **84** was soluble in dioxan and recrystallisation was easily accomplished to yield small single crystals. These were analysed via X-ray diffraction on the synchrotron source at the Daresbury Laboratory (DARTS) and structural refinement

was completed by Dr. Elizabeth MacLean (figure 106). From this analysis it was clear that methylation had occurred at both nitrogen and oxygen.

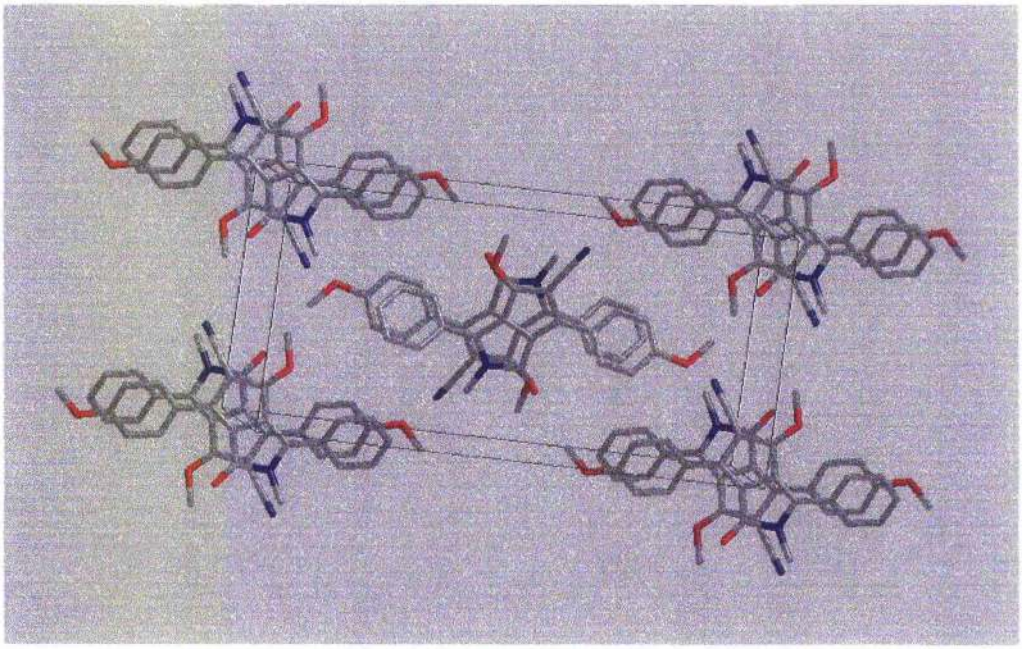
Figure 106: X-ray structure (full details available in Appendix 5 - page 169)





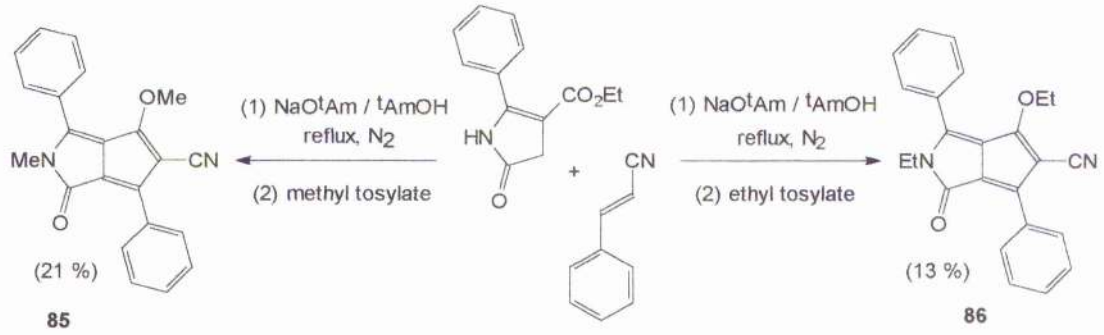
The X-ray data provided fully conclusive evidence to prove that the bicyclic ring structure and functionality of **84** were as predicted. From the crystal packing diagram (figure 107) it was also apparent that the molecules are π-π stacked within the crystal, with alternate molecules orientated at 180° to each other.

Figure 107: Crystal packing diagram



To extend this chemistry further, the similar *in situ* methylation of another compound in the series was completed to provide derivative **85**. Moreover, ethylation was readily accomplished when ethyl tosylate was employed in the reaction, affording the diethyl derivative **86**. The details of these reactions are summarised in figure 108.

Figure 108



4.3.3.4 Sublimation

Prior to the above investigation of the chemistry of the cyclopenta[*c*]pyrrol-1-one derivatives, the sublimation of these materials was attempted with the intention of depositing single crystals suitable for X-ray analysis. This, however, led to further reaction taking place. When the 4-chlorophenyl derivative **81b** was sublimed *in vacuo* at over 200 °C during several hours, a brown-red solid was obtained with complete volatilisation of the starting compound. ^{1}H NMR indicated that this was not starting material, but elemental analysis was consistent with an isomer of the starting reagent. The UV-VIS spectrum was characteristically different from that of the parent compound. Single crystals of this material were isolated and X-ray analysis (figure 110) provided complete structural characterisation as the compound **87**. Skeletal rearrangement had occurred via rupture of the dotted bond shown in **81b** (figure 109) below.

Figure 109

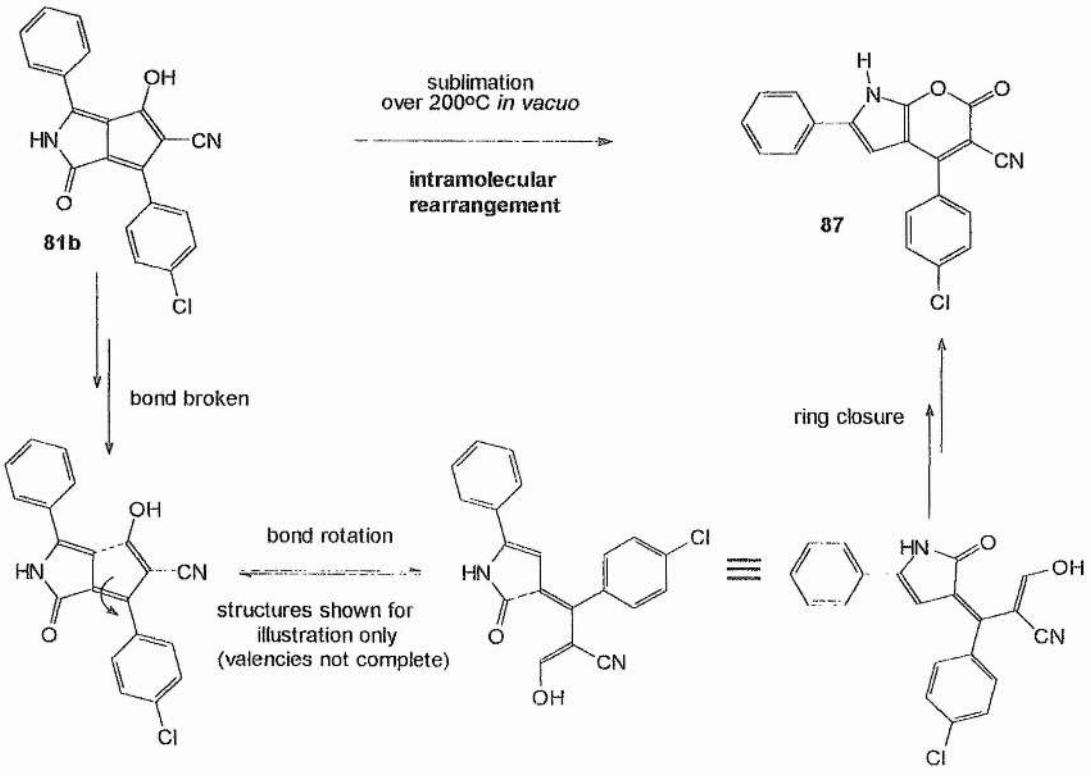
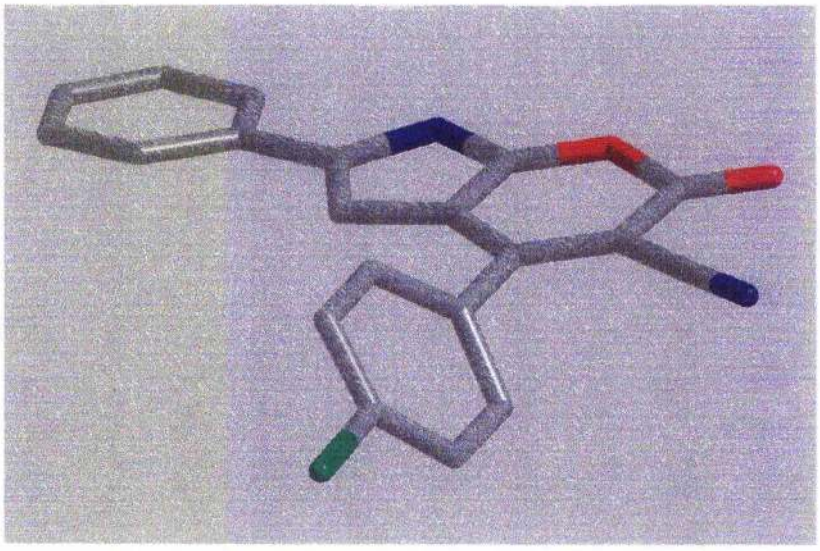
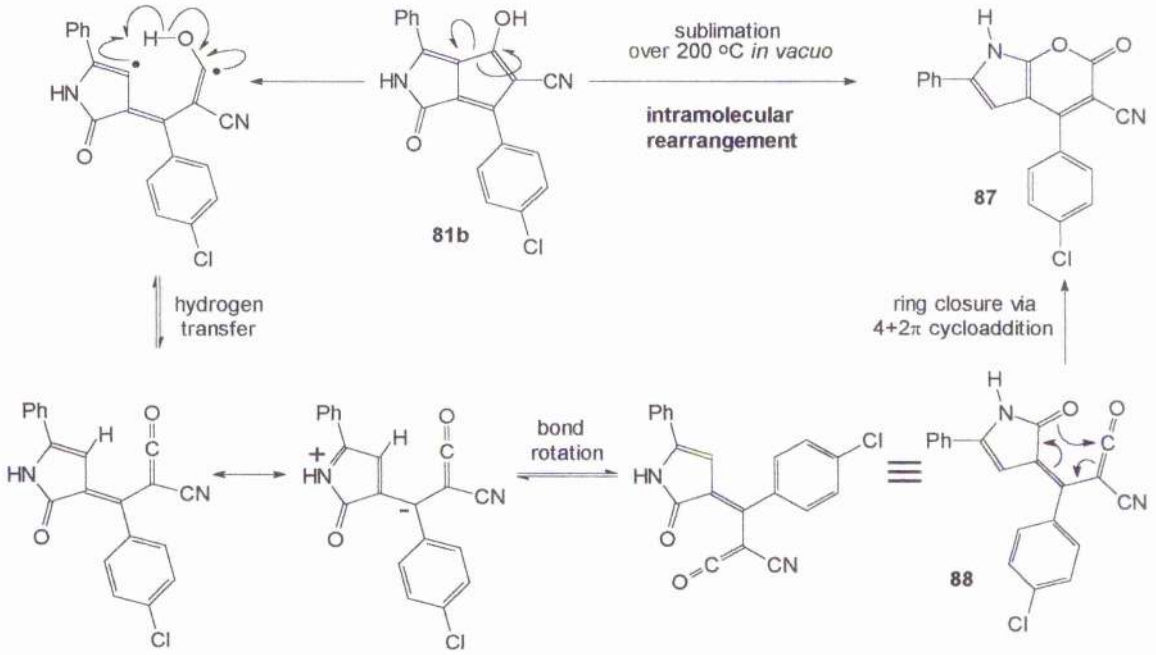


Figure 110: X-ray structure (full details available in Appendix 6 - page 174)



It is presumed that unimolecular, intramolecular rearrangement must have occurred in the gas phase to provide this product. This rearrangement would require the breaking of the bond highlighted in figure 109, with subsequent ring closure to produce the observed structure **87**. This reaction could have occurred via an electrocyclic process, but could equally have resulted from a stepwise ring opening then ring closure. One possible mechanism for this reaction is shown in figure 111 below, commencing with a radical ring opening then hydrogen transfer to produce a highly reactive ketene intermediate **88**. This could then ring close in a $(4 + 2)\pi$ cycloaddition to yield the product **87**.

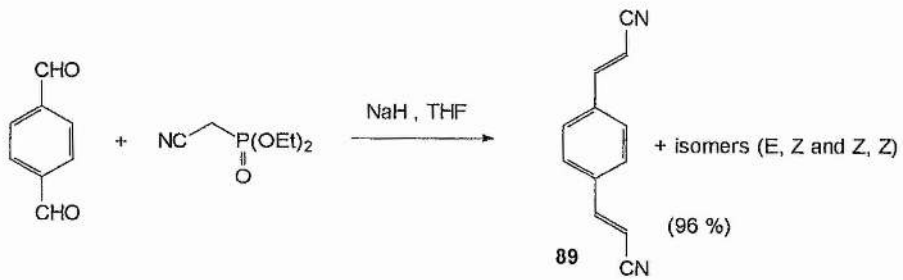
Figure 111



4.3.3.5 3,3'-(*p*-Phenylenebis)acrylonitrile

The synthesis of the 1,4-dinitrile **89** was accomplished via a modification of literature[110] procedures: the reaction of 1,4-phthalic dialdehyde with diethyl cyanomethylphosphonate in tetrahydrofuran using sodium hydride as base. The colourless product was readily recrystallised from aqueous ethanol.

Figure 112



The reaction of **89** with the lactam ester **35** in sodium *t*-amyloxide yielded a highly insoluble purple solid. From the evidence available it is not yet clear if reaction has occurred at one or both reactive sites, or if a mixture was produced. The objective in conducting this reaction was to prepare a cross-conjugated, intensely coloured derivative and it was hoped that the increased molecular weight would serve to reduce the solubility. This reaction would, however, require further development work.

4.3.3.6 *In situ* alkylation with an alternative reagent

It was reported above that methylation at both the nitrogen and oxygen positions in the cyclopenta[*c*]pyrrol-1-one derivatives was readily accomplished by *in-situ* methylation with methyl tosylate under reflux. In the course of these methylation studies, the reaction of the lactam ester **35** with cinnamonitrile was repeated, but the mixture was quenched instead with methyl iodide. These conditions afforded an orange solid which ^{1}H and ^{13}C NMR showed was clearly not the same product as that obtained from the methyl tosylate quench. Instead, a single methyl resonance observed in the ^{1}H NMR spectrum (δ_{H} 1.90) indicated that *C*-methylation had occurred rather than *N*- or *O*-methylation. Furthermore, elemental analysis was consistent with a mono-methylated product, infra-red analysis showed a weak absorption at 3167 cm^{-1} (N-H) and mass spectral analysis augmented this evidence

with a large peak at 326 a.m.u.. This data would suggest the structure **90a** (figure 113). However, a trace amount of impurity was apparent from a very small singlet resonance in the ^{1}H NMR (δ_H 3.32, NCH_3) and a small peak was observed at m/z 340 in the mass spectrum, consistent with a dimethylated product. Attempts at recrystallisation did not afford crystals of sufficient quality for X-ray analysis.

When the reaction was scaled up to obtain further material for analysis, the reaction mixture was allowed to stir for several days after addition of methyl iodide, much longer than above. Interestingly, the material obtained upon work-up was orange, strongly fluorescent and was more readily recrystallised. X-ray analysis of this material was accomplished by Dr. A. Slawin (University of St. Andrews) despite the complication presented by disorder throughout the crystal structure. The structure refined with a chiral space group as compound **90b** (figure 113), but in view of the disorder it was not possible to either assign the stereochemistry of the molecule, or to confirm that it was a racemate. It was unambiguous in this case that dimethylation had occurred at both carbon and nitrogen. In addition, the infra-red spectrum showed no absorption consistent with an N-H bond and the ^{1}H NMR analysis was characteristically different to **90a**: two methyl resonances (δ_H 1.87 and 3.32) were observed in equal measure and the aromatic region was subtly different, the ortho hydrogens now shifted from before.

Figure 113

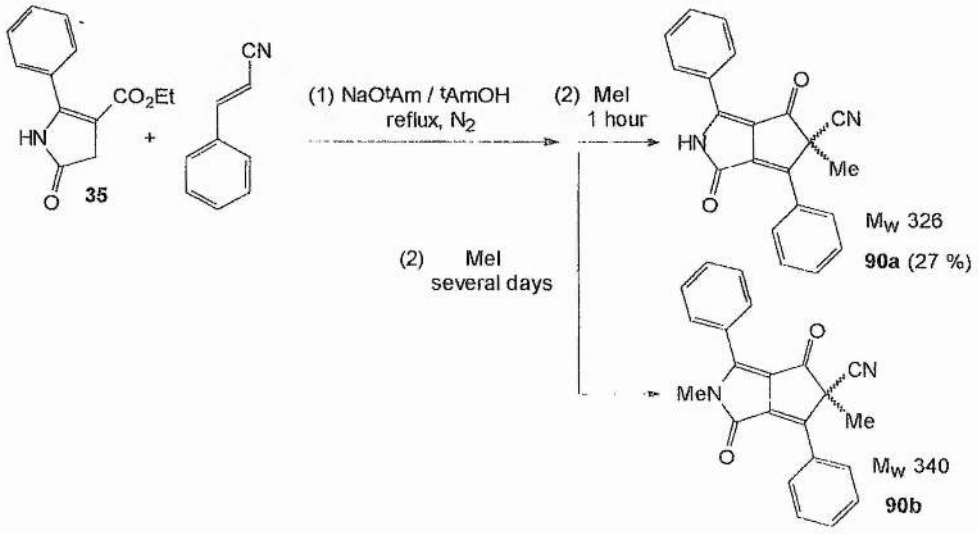
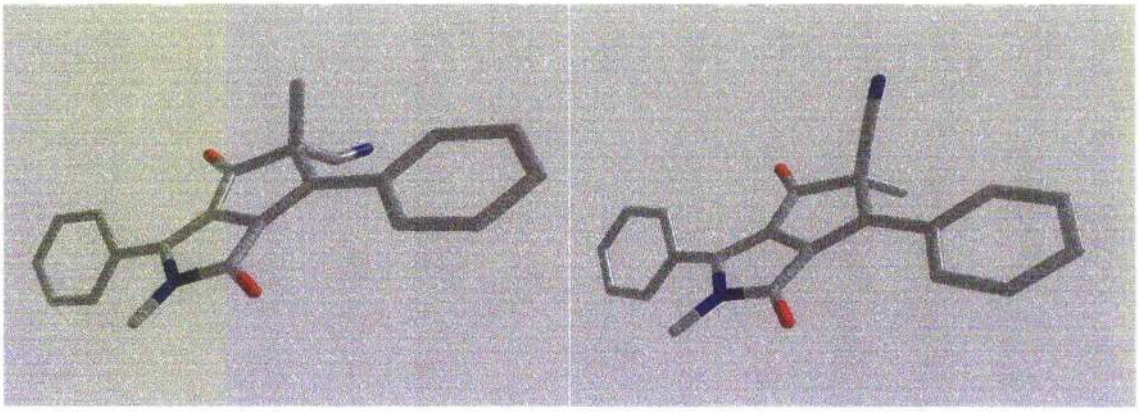


Figure 114: X-ray structure **90b** (full details in Appendix 10, page 200) - stereochemistry not assigned

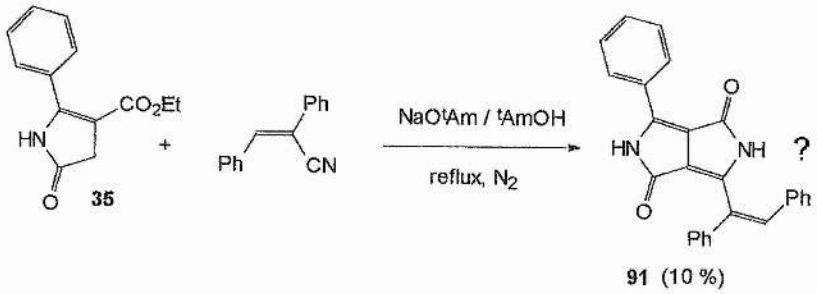


It is apparent from the X-ray structural data that the molecules are arranged in planes, with a degree of π-π interaction between the molecular planes. The methyl and nitrile groups about the tetrahedral carbon do, however, partly disrupt the close stacking of the molecules. The difference between the outcome of this reaction with methyl iodide and the aforementioned reactions with methyl tosylate could be explained by the softer electrophilic nature of methyl iodide relative to methyl tosylate, leading to substitution at the carbon rather than the oxygen or nitrogen nucleophilic centres.

4.3.3.7 The reaction of α-phenylcinnamonitrile

Lastly, the reaction of the lactam ester **35** with α-phenylcinnamonitrile was completed under reflux to afford a rich purple-coloured solid. This was highly insoluble in common organic solvents and so NMR data were not readily obtained. Accurate mass spectral data were consistent with the DPP structure **91** shown (figure 115). The material was purified extensively by heating under reflux in methanol then washing with water, but a sample of sufficient purity could not be produced for correct elemental analysis. The sample did not melt, presumably due to inorganic impurities or intermolecular hydrogen bonding.

Figure 115



91 (10 %)

Chapter 5

CINNAMATE ESTERS IN THE STANDARD DPP SYNTHESIS

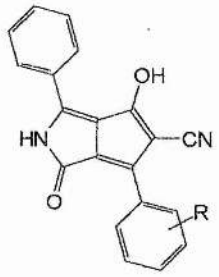
5.1 Introduction

Strategies for the synthesis of alkenyl-DPPs have been discussed throughout this thesis and the discovery of a novel family of cyclopenta[*c*]pyrrol-1-one derivatives was described in Chapter 4. The discovery arose from the attempted reaction of cinnamonitriles in the standard DPP synthesis. This chapter comprises an investigation into the similar reaction of cinnamate esters with the lactam ester **35**.

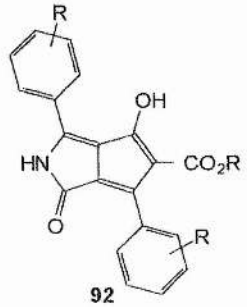
5.2 Cinnamate esters

The reaction of substituted cinnamonitriles with the lactam ester **35** afforded the products **78** and **81a-e** (figure 116). The corresponding reaction of the lactam ester **35** with cinnamate esters was considered worthy of investigation because it was envisaged that a series of similar products **92** containing an ester group could be prepared. These may demonstrate potential for application as pigments.

Figure 116



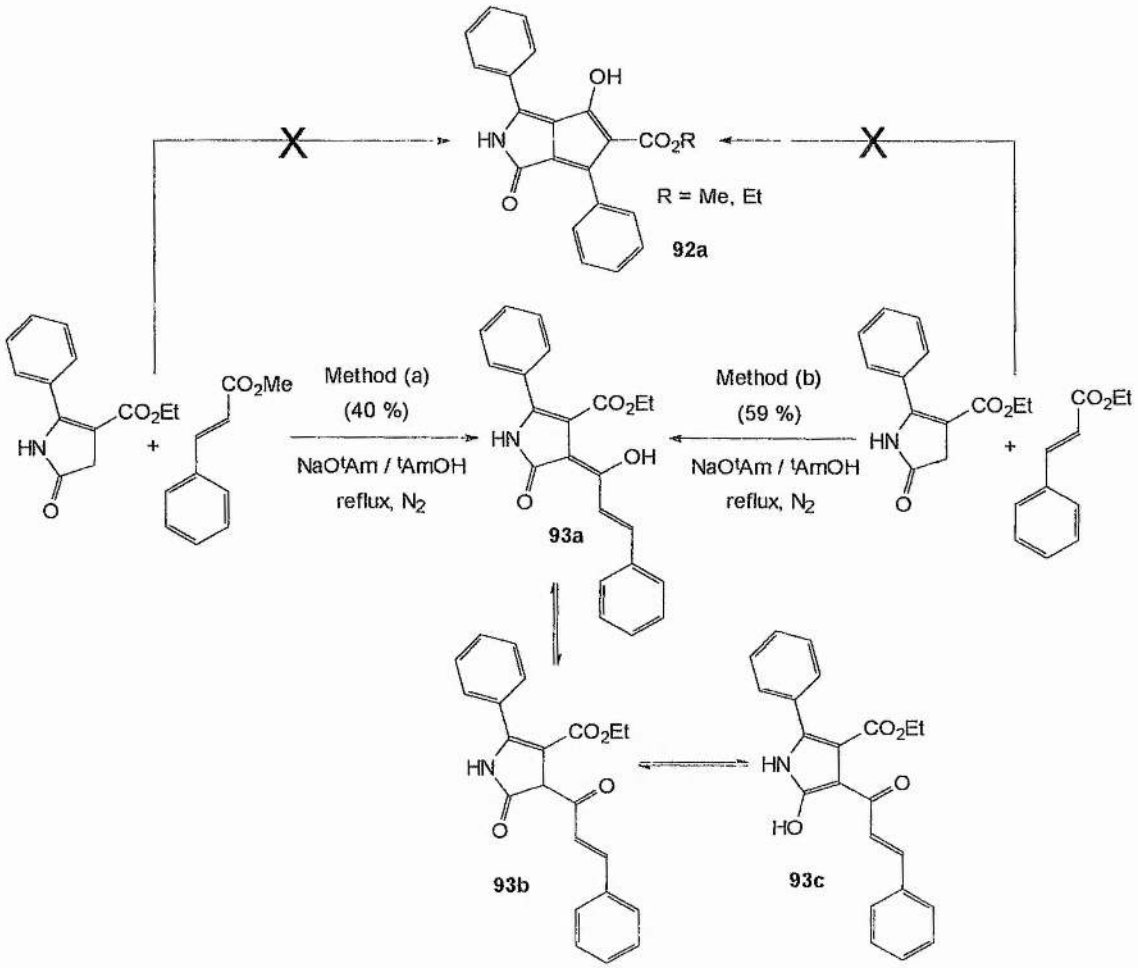
78 and **81a-e**



92

The reaction of the lactam ester **35** with ethyl cinnamate was first completed in sodium *t*-amyloxide under reflux and proceeded to give a bright orange product (figure 117). ^{1}H NMR and infra-red analysis confirmed that this product contained both an ethyl ester and amide functionality, but mass spectral data indicated a molecular mass of 361. This was not consistent with the expected product **92a** (molecular mass 359). The ^{1}H NMR spectrum also indicated that the carbon-carbon double bond of the cinnamate had been retained in the product. However, the source of the ester group was not clear; did it originate from the lactam ester **35** or from ethyl cinnamate?

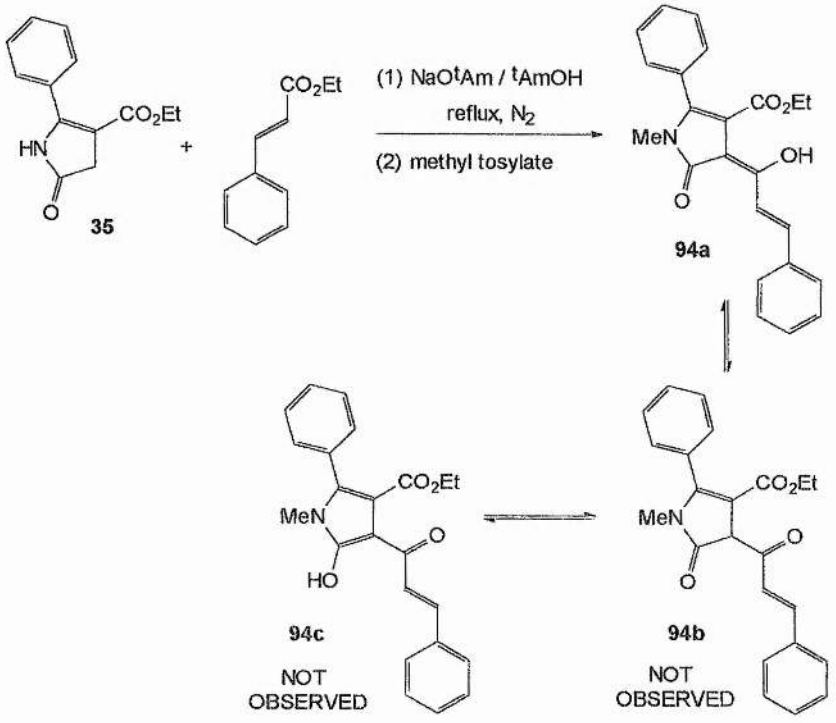
Figure 117



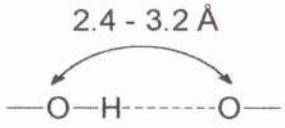
To further probe this problem, the reaction of the lactam ester **35** with methyl cinnamate was completed (figure 117) and a bright orange product was isolated; it was chemically identical with the compound obtained from the reaction of ethyl cinnamate. This evidence now proved that the ester observed in the product had originated from the lactam ester reagent. Consequently, structure **93** was proposed for the product (figure 117), the result of a 1,2-addition of the lactam ester anion to the cinnamate ester functionality (in effect a Claisen acylation reaction) followed by the loss of an alkoxide leaving group. This structure could exist as any one of three tautomers **93a-c**. To investigate further which tautomer was favoured, X-ray structural analysis was required, but it was not possible to obtain suitable crystals via recrystallisation.

In a fashion similar to the work described previously for the reactions of cinnamonitriles, an *in situ* methylation was completed, following the procedure tested for diphenyl-DPP (figure 105, page 73). Hence, when the lactam ester **35** was reacted with ethyl cinnamate in sodium *t*-amyloxide, and the reaction then quenched with methyl tosylate, an orange solid was isolated (figure 118). This was soluble in common organic solvents and was readily recrystallised to provide single crystals for X-ray analysis, so overcoming the problem of characterisation.

Figure 118

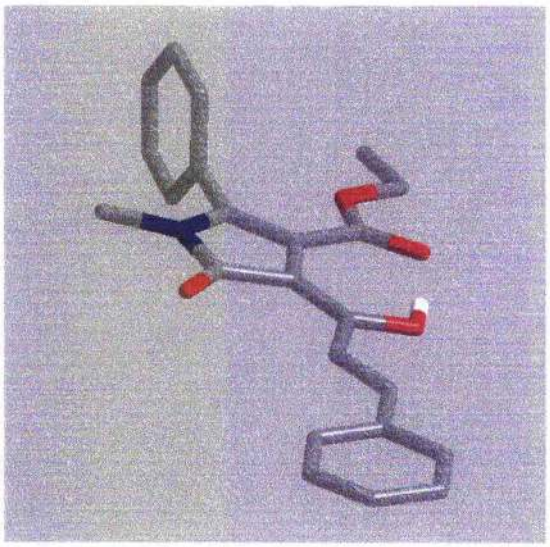


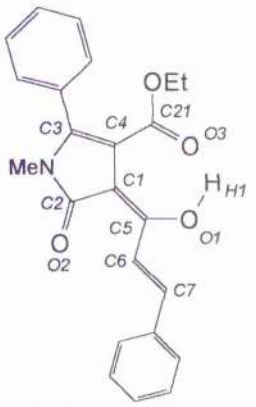
It was clear from the X-ray data (summarised in figure 119 with numbering scheme) that C1-C5, C2-O2 and C6-C7 were all short, consistent with double bonds, whilst C1-C2 and C5-O1 were single bonds, confirming that in the solid state at least, the enol tautomer **94a** was obtained. The torsion and bond angles highlighted that the hydroxyl group of the enol was aligned with the ester functionality in an essentially planar configuration. Furthermore, the interatomic distance O1-O3 was only 2.51 Å. From the literature[111-112] it was recognised that an O-O distance (as defined below) in the range 2.4-3.2 Å was indicative of a hydrogen bonding interaction. It is normal to refer to the O-O distance rather than the O-H distance for reasons of accuracy.



Therefore, the relatively short O1-O3 distance was evidence for a hydrogen bonding interaction between O1 and O3, with a seven-membered ring apparent (i.e. H1-O1-C5-C1-C4-C21-O3). This was a surprising result given the opportunity available to form a stable six-membered hydrogen bonded ring with the amide carbonyl O2 (i.e. H1-O1-C5-C1-C2-O2).

Figure 119: X-ray structure with selected data shown (full details available in Appendix 7 - page 181)





numbering consistent
with ORTEP diagram in Appendix 7

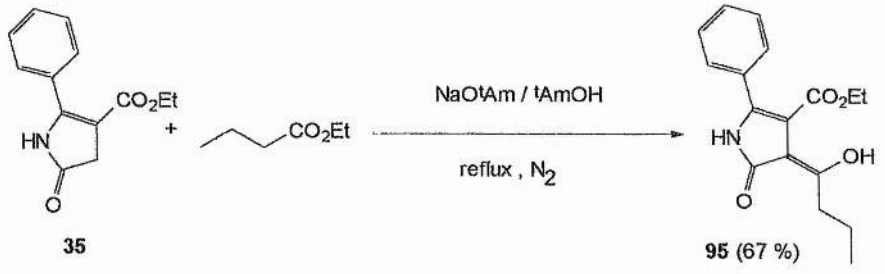
atoms	distance (Å)
C1 - C5	1.383
C5 - C6	1.448
C6 - C7	1.331
C2 - O2	1.235
C5 - O1	1.330
O1 - O3	2.51

atoms	torsion angle (°)
O1 - C5 - C1 - C4	-0.6
O3 - C21 - C4 - C1	-2.2
O1 - C5 - C1 - C2	178.8

atoms	bond angle (°)
C5 - O1 - H1	109.5
C4 - C1 - C5	130.2
O3 - C21 - C4	124.7
O1 - C5 - C1	122.5

Both alkyl and aryl esters were then reacted with the lactam ester **35** to examine whether the outcome of the cinnamate ester reactions above could be generalised. The reaction of ethyl butyrate with the lactam ester **35** in sodium *t*-amyloxide was first completed and yielded a near colourless solid (figure 120). This was recrystallised to provide single crystals for X-ray analysis, which showed the product was similar to that obtained in the case of ethyl and methyl cinnamate (figure 117), containing a planar pyrrolinone ring with a γ-keto ester functionality incorporated.

Figure 120

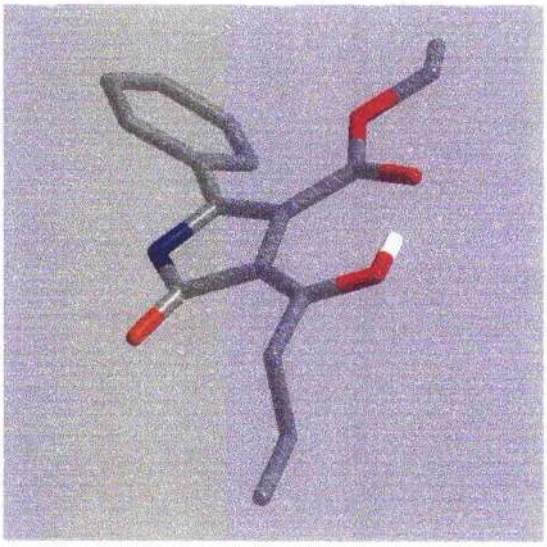


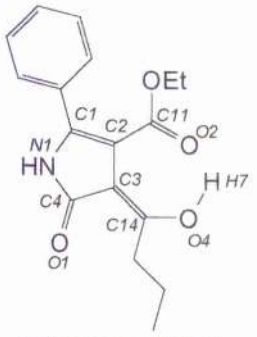
35 **95** (67 %)

The X-ray details are summarised in figure 121 below: the selected interatomic distances shown indicate that C4-O1 and C3-C14 are short, consistent with double bonds whilst C14-O4 and C3-C4 are longer, consistent with single bonds. These bond distances correspond with the enol tautomer **95**.

It is also apparent from the selected torsion and bond angles shown that the hydroxyl and ester groups are aligned with each other, in an essentially planar arrangement. The short O2-O4 distance (2.52 Å) further indicated a hydrogen bonding interaction, as described in the previous example, to complete a seven-membered ring (H7-O4-C14-C3-C2-C11-O2).

Figure 121: X-ray structure with selected data shown (full details available in Appendix 8 - page 188)





numbering consistent
with ORTEP diagram in Appendix 8

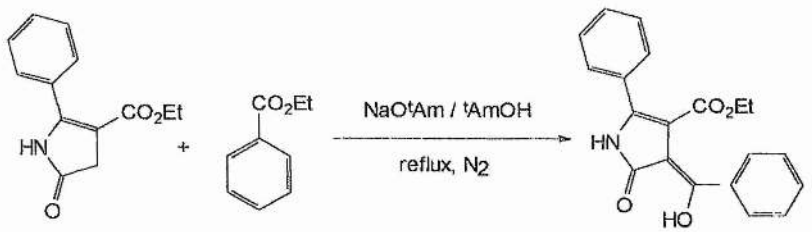
atoms	distance (Å)
C3 - C14	1.367
C4 - O1	1.243
O4 - C14	1.322
C3 - C4	1.455
O2 - O4	2.52

atoms	bond angle (^{O})
C14 - O4 - H7	109
C2 - C3 - C14	132.2
O2 - C11 - C2	125.1
O4 - C14 - C3	124.2

atoms	torsion angle (^{O})
O4 - C14 - C3 - C2	0.0
O2 - C11 - C2 - C3	4.9
O4 - C14 - C3 - C4	-177.8

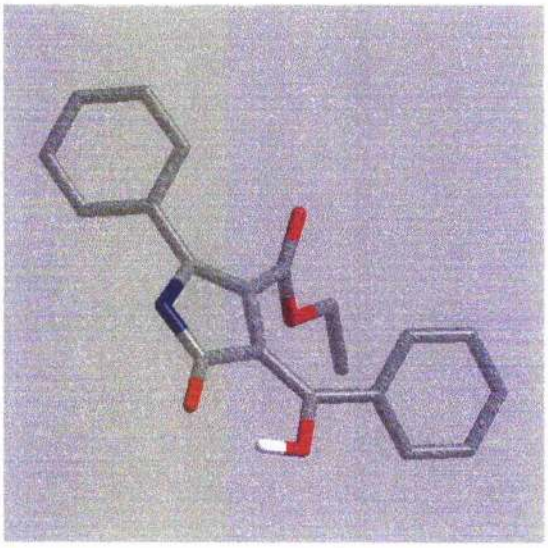
Lastly, the reaction of the lactam ester **35** with ethyl benzoate in sodium *t*-amyloxide was completed (figure 122) and yielded a beige coloured product, which was recrystallised to provide single crystals for X-ray analysis. The data summarised below (figure 123) showed that O1-C4 and C3-C14 were short, consistent with double bonds and that C3-C4 and O4-C14 were longer, consistent with single bonds. This indicated that the enol tautomer **96** was obtained, as observed in the previous examples. However, it was clear from the selected torsion and bond angles that the hydroxyl group of the enol was aligned with the amide carbonyl O1 in an essentially planar arrangement rather than with the ester carbonyl O2. The relatively short O1-O4 distance (2.57 Å) further provided evidence for a hydrogen bonding interaction, but with a six-membered hydrogen bonded ring (H17-O1-C4-C3-C14-O4) apparent in this case. This is markedly different to the earlier results for cinnamate esters (figure117 and 118) and ethyl butyrate (figure 120). An explanation for the observed disparity between the six and seven membered hydrogen bonded ring formation is not yet obvious.

Figure 122



35 **96** (33 %)

Figure 123: X-ray structure with selected data shown (full details available in Appendix 9 - page 194)



numbering consistent
with ORTEP diagram in Appendix 9

atoms	distance (Å)
C3 - C14	1.372
C4 - O1	1.260
O4 - C14	1.342
C3 - C14	1.447
O1 - O4	2.57

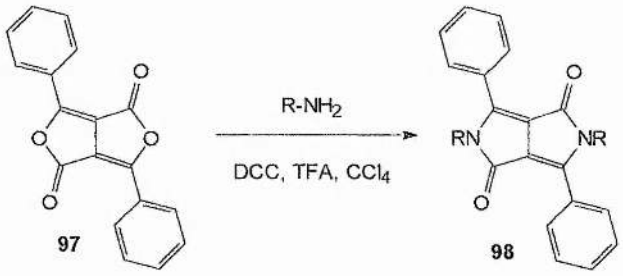
atoms	torsion angle (°)
O1 - C4 - C3 - C14	-3.9
O4 - C14 - C3 - C4	6.3
O4 - C14 - C3 - C2	-176.0

atoms	bond angle (°)
C14 - O4 - H17	108
C14 - C3 - C4	119.4
O1 - C4 - C3	127.8
O4 - C14 - C3	118.9

5.2 Relevance to DPP chemistry and possible future work

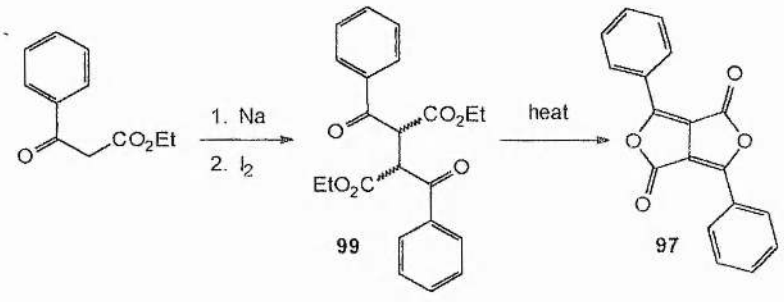
In Chapter 1 (page 14), a recently reported synthesis of *N*-arylated DPPs was described, namely the reaction of a dilactone such as **97** with a primary aromatic amine in the presence of DCC. This yielded intensely fluorescent products such as **98** (figure 124), which were readily soluble in common organic solvents.

Figure 124



The diketofurofuran **97** was prepared in the literature[113] from the corresponding benzoylacetic ester, which was oxidatively dimerised with iodine[114] to a mixture of the *meso* and racemic form of compound **99**, followed by heating to afford **97** (figure 125). Rubin and co-workers[115] reported a similar cyclisation of dialkyl 2,3-bisbenzoylsuccinates such as **99**. Langhals *e. al.*[32] also reported that the synthesis of **97** was better achieved when the racemic product **99** was isolated then cyclised to **97** at 280 °C.

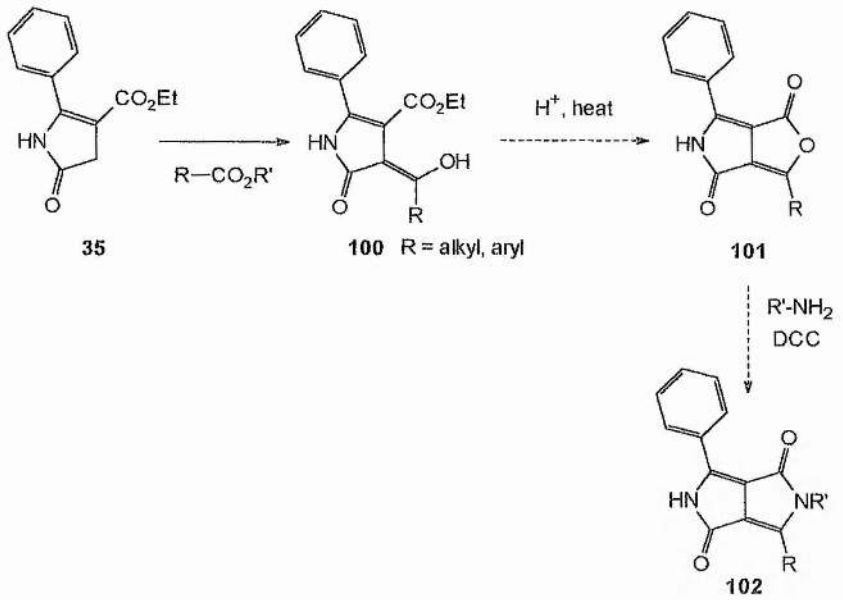
Figure 125



The results of the reactions of cinnamate, alkyl and aryl esters with the lactam ester **35** described previously in this chapter have provided a series of substituted lactam ester derivatives **100** (figure 126). It was envisaged that these derivatives could be ring closed upon heating with acid catalysis to furnish the mono-lactones **101**, in a similar manner to the ring closure outlined above This would provide a synthetic route to monoarylated DPPs **102**. Such products could display interesting properties,

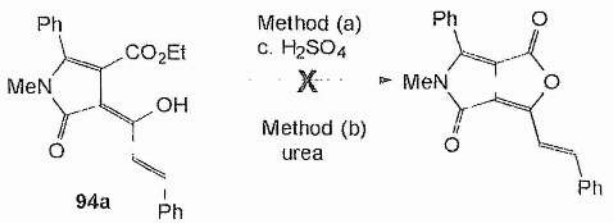
with one amide proton still retained to impart hydrogen bonding and lower the solubility. The X-ray analyses described earlier (figures 119 and 121) for the products **99** arising from the ethyl butyrate and cinnamate ester reactions further indicate that the hydroxyl groups were orientated cis to the ester functionality. This would favour ring closure to the mono-lactone materials **100**.

Figure 126



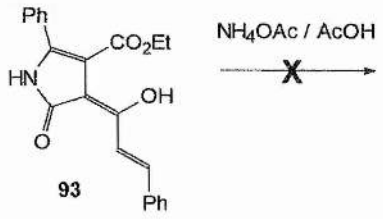
Preliminary results in the laboratory, however, indicated that the ring closure of compounds **100** was not straightforward to accomplish in practice. The reaction of the product **94a** with concentrated sulfuric acid at elevated temperatures yielded an orange tacky solid which could not easily be purified (figure 127). The material isolated was partly soluble in water and it was suspected that partial sulfonation of the phenyl rings had occurred. When the reaction was repeated in concentrated orthophosphoric acid with heating, only unreacted starting material was similarly recovered.

Figure 127



Instead, the possibility of effecting a ring closure with an ammonia equivalent was investigated, in the hope of directly preparing a DPP product. To this end, a sample of the product **94a** was heated with urea to 145 °C for several hours (figure 127), but no reaction was observed. In view of this result, the original synthesis of the lactam ester **35** from diethyl benzoylsuccinate (figure 50, page 38) suggested the use of ammonium acetate in acetic acid as a suitable ammonia equivalent. When a sample of compound **93** was heated to reflux in such a mixture during several hours (figure 128), subsequent work-up showed that no ring closure had ensued, with only unreacted starting material apparent from the ^{1}H NMR. These results are surprising in view of the geometry of hydroxyl and ester groups in the starting materials, and the elevated temperatures employed for reaction. Further work would be required to find conditions suitable for ring closure and to develop the potential of this new chemistry.

Figure 128



Chapter 6

EXPERIMENTAL

6.1 Apparatus

Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FT spectrophotometer; solids were recorded as Nujol mulls and all liquids were recorded as thin films. UV-VIS spectra were recorded on a Philips PU-8730 spectrophotometer. Mass spectra and accurate mass measurements were obtained using a A.E.I. / Kratos M.S.-50 spectrometer and all spectra were obtained using EI (electron impact ionisation) (70 eV). Elemental analyses for carbon, hydrogen and nitrogen were carried out using a Carlo-Erba 1106 elemental analyser.

^{1}H and ^{13}C NMR spectra were those obtained at either 300 MHz or 75.4 MHz, respectively, for solutions in $CDCl_3$ unless indicated otherwise; chemical shifts are expressed in ppm units relative to $SiMe_4$ ($\delta_H=\delta_C=0$) and coupling constants (J) in Hz. Where indicated, only partial NMR assignments are reported for some compounds; all other spectral features are in agreement with the proposed structures. Abbreviations for NMR results are; singlet (s), doublet (d), double doublet (dd), multiplet (m), double triplet (dt) and broad (br).

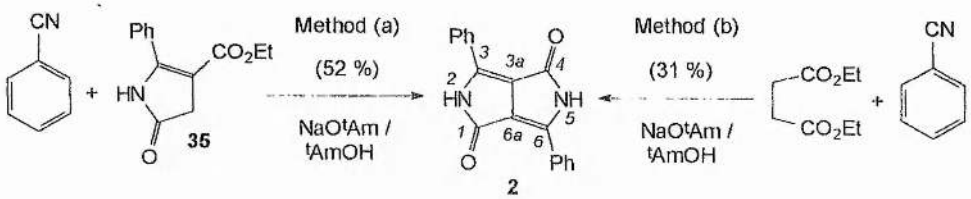
Thin layer chromatography was completed using 0.2 mm layers of silica (Merck, Kieselgel $60F_{254}$) on polyester sheets and the components observed under ultraviolet light. Dry flash chromatography was carried out using Fluka Kieselgel II (5-40 μm particle size) unless indicated otherwise.

Commercially available solvents were used without further purification unless otherwise stated. The term 'petrol' refers to the fraction of b.p. 40-60 °C. Dry ethanol was prepared by heating a suspension of magnesium ethoxide and ethanol for 1 h followed by distillation on to activated 4 Å molecular sieves. Dry ether and tetrahydrofuran were prepared by the addition of sodium wire followed by distillation. Dry dichloromethane was distilled from phosphorus pentoxide and stored over 4 Å molecular sieves. Triethylamine was dried and purified by heating under

Dry DMF was prepared by heating a suspension of DMF and calcium hydride to 130 °C for 1 h before distillation, under reduced pressure, on to 4 Å molecular sieves. *t*-Amyl alcohol was dried and purified by heating to reflux with sodium metal for several hours followed by distillation on to 4 Å molecular sieves.

Appendices 1-10 (page 144) contain the details of all the X-ray crystal data, the data collection and the refinements. The systematic absences allowed unique assignment of all the space groups. All intensity data were recorded at 293(1) K with a Rigaku AFC7S diffractometer (except for appendices 5 and 10) using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å). For the results reported in Appendices 5 and 10 only (i.e. compounds **84** and **90**), the intensity data were recorded at 293 K with a Siemens SMART CCD diffractometer employing ω rotation with narrow frames. Unless indicated otherwise, the structures were solved by direct methods using SIR92[116] and refined by full-matrix least squares on F, using the TEXSAN system 1.[117] All hydrogen atoms were located from difference maps, and were included in the refinements as riding atoms in idealised positions with isotropic displacement parameters; all non-hydrogen atoms were refined anisotropically. The structural diagrams included in the appendices were prepared using ORTEPII[118].

6.2 Experimental for Chapter 2

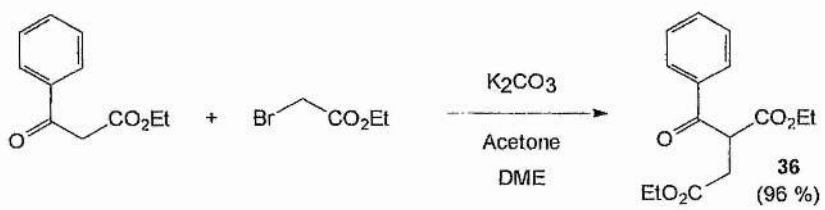


3,6-Diphenyl-DPP 2

Method (a) To pre-dried *t*-amyl alcohol (15 ml) was added sodium (0.14 g, 0.0061 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. Benzonitrile (0.23 g, 0.0022 mol) then the lactam ester **35** (0.37 g, 0.0016 mol) were added upon which a red precipitate rapidly formed. The mixture was heated under reflux for 2 h, cooled and added portionwise to an ice-

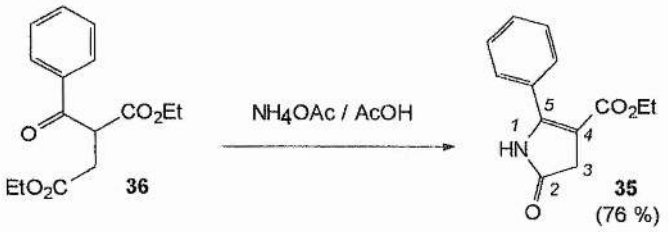
mixture was heated under reflux for 2 h, cooled and added portionwise to an ice-cooled mixture of methanol (5 ml) and concentrated hydrochloric acid (1 ml). The bright red precipitate was filtered off, washed with methanol and water then dried *in vacuo*. Yield 0.24 g (52%).

Method (b) To pre-dried *t*-amyl alcohol (45 ml) was added sodium (0.5 g, 0.0217 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. Benzonitrile (2.24 g, 0.0217 mol) was added, then diethyl succinate (1.89 g, 0.0108 mol) was added portionwise over 4 h and heating continued for a further 1 h. The mixture was stirred for 16 h at 25 °C, then added to an ice-cooled mixture of concentrated hydrochloric acid (2.2 ml) and methanol (20 ml). The bright red precipitate was filtered off, washed with methanol and dried *in vacuo*. Yield 0.11 g (31%). The filtrate was shown by ^{1}H NMR to contain unreacted benzonitrile and diethyl succinate. ν_{max}/cm^{-1} 3070 and 3160 (N-H), 1640 (C=O), 1600 (N-H bending or Ar-C-C stretch). *m/z* 288.0909 ($M^{+\cdot}$, 100%; $C_{18}H_{12}N_2O_2$ requires 288.0899), 258 (25), 230 (41), 104 (72), 77 (63).



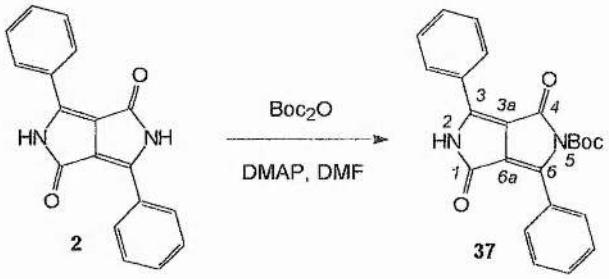
Diethyl benzoylsuccinate 36

Ethyl bromoacetate (15.12 g, 0.1001 mol) was added to a stirred mixture of potassium carbonate (13.82 g, 0.01 mol), acetone (50 ml), 1,2-dimethoxyethane (33 ml) and ethyl benzoylacetate (16.1 g, 0.0838 mol) at 40 °C over 20 min. The mixture was stirred at reflux until reaction was complete by tlc (approximately 9 h), then filtered and the filtrate concentrated under reduced pressure to give the crude product (22.36 g, 96%). Kugelrohr distillation yielded pure product (bulb temp. *ca.* 185-190 °C/0.3 mmHg; lit.,[119] b.p. 150-154 °C/8.1 mbar). δ_H (200 MHz; $CDCl_3$), 1.14 [3H, t, J 6.6, OCH_2CH_3], 1.21 (3H, t, OCH_2CH_3), 2.99 and 3.10 [each 1H, dd, J 7.2 (vicinal) and J 17.1(geminal), CH_2CO_2Et], 4.11 and 4.12 (each 2H, 2 overlaid q, 2 x OCH_2CH_3), 4.86 (1H, t, J 7.2, $CHCH_2CO_2Et$), 7.49 (3H, m, *m-/p-* Ar-H), 8.03 (2H, d, J 7.3, *o*-Ar-H).



4-Ethoxycarbonyl-5-phenyl-4-pyrrolin-2-one 35

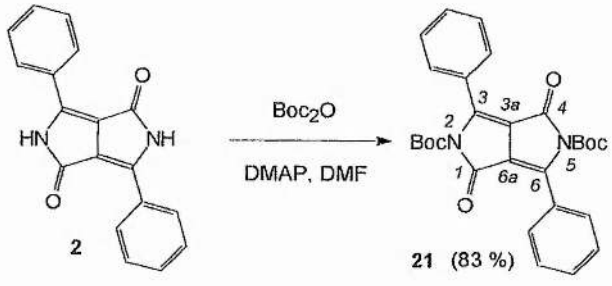
To a solution of ammonium acetate (28.07 g, 0.36 mol) in acetic acid (50 ml) at 70-80 °C under nitrogen was added diethyl benzoylsuccinate **36** (10.0 g, 0.036 mol). The mixture was heated to reflux (120 °C) with stirring for 6 h, then cooled to 90 °C and added to a well stirred, ice-water mixture. The green-yellow precipitate was filtered off, washed with water and dried *in vacuo* at 60 °C. Yield 6.35 g (76 %). Fibrous, beige crystals were obtained upon recrystallisation twice from ethanol / water (2:1), then from propan-2-ol: m.p. 172.5-173.5 °C (lit.[30] 174 °C). δ_H 1.17 (3H, t, J 6.6 Hz, OCH_2CH_3), 3.50 (2H, s, ring CH_2), 4.11 (2H, q, OCH_2CH_3), 7.45 (3H, m, *m-/p-* Ar-H), 7.57 (2H, m, *o-* Ar-H), 8.11 (br.s, NH). δ_C 14.02 (OCH_2CH_3), 38.73 (C-3), 60.00 (OCH_2CH_3), 104.37 (C-5), 128.25 and 128.79 (*o-/m-* Ar-C), 129.37 (*ipso* Ar-C), 130.65 (*p-* Ar-C), 151.52 (C-4), 163.34 (C-2), 177.93 (CO_2Et).



2-*t*-Butoxycarbonyl-3,6-diphenyl-DPP 37

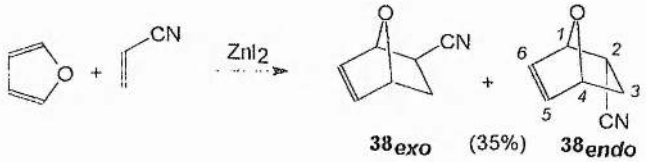
A mixture of 3,6-diphenyl-DPP **2** (0.2 g, 0.7 mmol), *N,N*-dimethylformamide (1.5 ml), DMAP (0.03 g, 0.2 mol) and Boc_2O (0.32 g, 0.15 mmol) was stirred at room temperature for 44 days. After 4 days, Boc_2O (0.32 g, 1.5 mmol) was added and at 24 days further Boc_2O (0.32 g, 1.5 mmol) and *N,N*-dimethylformamide (0.5 ml) were added. The reaction mixture was filtered through a short silica column and excess water added to the filtrate. The orange-red precipitate was filtered off and dried *in vacuo*. Yield 0.02 g (7%). The product decomposed without melting. δ_H (200 MHz) 1.41 [9H, s, $C(CH_3)_3$], 7.47-7.54 (8H, m, Ar-H), 7.75-7.78 (1H, m, Ar-H), 8.26-8.29

(1H, m, Ar-H), 9.35 (1H, br. s, NH). δ_C (50.3MHz) 27.51 [OC(CH_3)$_3$], 84.94 [OC(CH$_3$)$_3$], 107.79, 115.14 (C-3 and -6), 127.13, 128.15, 128.40, 128.50, 128.68, 129.16, 131.20, 132.61 (Ar-C), 144.73, 146.46, 148.50 (C-1, -3a, and -6a), 159.50 (C-4), 164.04 [CO$_2$C(CH$_3$)$_3$].



2,5-Bis-*t*-butoxycarbonyl-3,6-diphenyl-DPP 21[119]

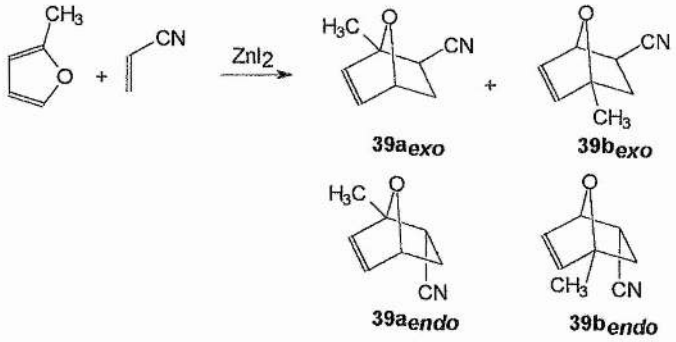
A mixture of 3,6-diphenyl-DPP **2** (0.49 g, 1.7 mmol), tetrahydrofuran (25 ml), DMAP (0.08 g, 0.0007 mol) and Boc$_2$O (1.23 g, 5.6 mmol) was stirred at room temperature for 24 h. Further Boc$_2$O (0.4 g, 1.8 mmol) was added and stirring continued for 2.5 h. The reaction mixture was concentrated, the residual moist brown solid mixed with methanol (1 ml), filtered off and washed with methanol (2 ml). The light yellow product (0.69 g, 83%) was dried *in vacuo*. The product decomposed without melting over the range 185-236 °C (by DSC). λ_{max}/nm (acetonitrile) 423.8 (ε 10625). δ_H (200 MHz) 1.38 [18H, s, C(CH_3)$_3$], 7.46-7.51 (6H, m, *m-/p-* Ar-H), 7.72-7.76 (4H, m, *o-* Ar-H). δ_C 27.40 [OC(CH_3)$_3$], 85.22 [OC(CH$_3$)$_3$], 112.25, 112.43 (C-3 and *ipso* Ar-C), 128.45, 128.55 (*o-/m-* Ar-C), 131.61 (*p-* Ar-C), 146.41, 148.16 (C-3a and -1), 159.54 [COC(CH$_3$)$_3$].



7-Oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile 38[70]

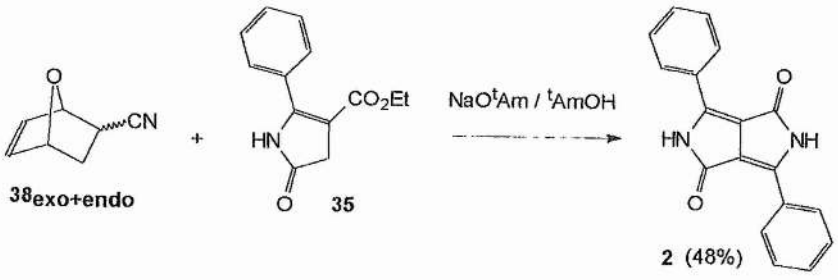
A mixture of furan (10.05 g, 0.1476 mol), acrylonitrile (6.62 g, 0.1248 mol) and zinc iodide (2.0 g, 0.0063 mol) was stirred at 40-60 °C for 48 h. The light brown mixture was then diluted with ethyl acetate, washed with 0.1 M sodium thiosulfate (2x10 ml) and concentrated. Column chromatography on silica gel (30-70 grade) eluted with

petrol / ethyl acetate (2:1) yielded the adduct **38** (5.36 g, 35%), b.p. 110-115 °C/0.3 mmHg, as an *exo/endo* mixture. ν/cm^{-1} 2244 (C≡N). δ_H (assigned with aid of COSY) *Exo* adduct: 1.77 (1H, dd, J 8.5 and 11.5, H-3), 2.14 (1H, m, H-3'), 2.41 (1H, dd, J 4.0 and 8.4, H-2), 5.19 and 5.24 (1H, m, H-1 or 4), 6.32 (1H, dd, H_{5or6}), 6.44 (1H, dd, $J_{1,6}$ 1.7 and $J_{5,6}$ 5.8, H_{5or6}). *Endo* adduct: 1.56 (1H, dd, J 3.6 and 11.5 , H-3), 2.31 (1H, m, H-3'), 2.94 (1H, dt, J 4.0 and 9.6, H-2), 5.15 (1H, m, H-1 or 4), 5.24 (1H, m, H-1 or 4), 6.50 (1H, dd, H-5 or 6), 6.58 (1H, dd, $J_{1,6}$ 1.7 and $J_{5,6}$ 5.8, H-5 or 6). *Exo:endo* ratio approx 4-3.



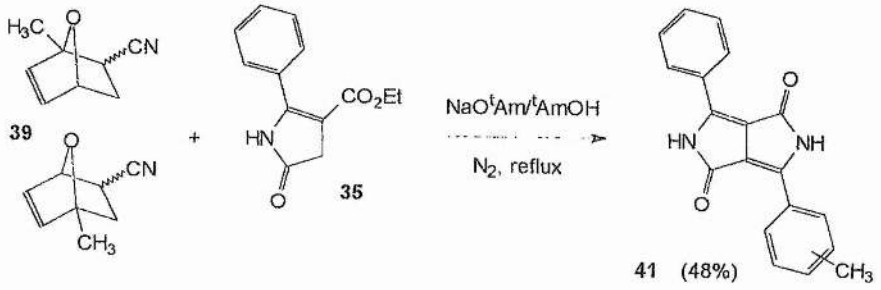
Diels-Alder adduct of 2-methylfuran and acrylonitrile 39

A mixture of 2-methylfuran (10.0 g, 0.1218 mol), acrylonitrile (12.93 g, 0.2437 mol) and zinc iodide (2.02 g, 0.0063 mol) was stirred at 50 °C for 9 h, then at 25 °C for 5 days. The light brown mixture was then diluted with ethyl acetate, washed with 0.1 M sodium thiosulfate then water, dried and concentrated (crude yield 9.86 g, 60%). Column chromatography of a small portion on silica gel H eluted with petrol / ethyl acetate yielded pure adduct. ν_{max}/cm^{-1} 2250 (C≡N). The product was a mixture of 2 constitutional isomers **39a+b**, each themselves consisting of an *exo/endo* mixture. A complete assignment was not possible due to the complexity of the isomer mixture, but the alkenic protons H-5 and H-6 provided limited information, confirming the presence of 4 isomers: δ_H 1.61-1.69 (m), 1.76 (s), 1.81 (s), 1.83-1.92 (m), 1.97-2.04 (m), 2.20-2.29 (m), 2.39-2.52 (m), 2.63 (dd, J 3.7 and 9.4), 3.04-3.10 (m), 5.01-5.07 (m), 5.12-5.14 (m), 6.11 (d), 6.25 (d), 6.30 (d), 6.38 (d, J 5.6), 6.42 (dd), 6.47 (dd), 6.55 (dd, J 1.6 and 5.8). Assignment of an isomer ratio was not possible.



Reaction of nitrile 38 and the lactam ester 35

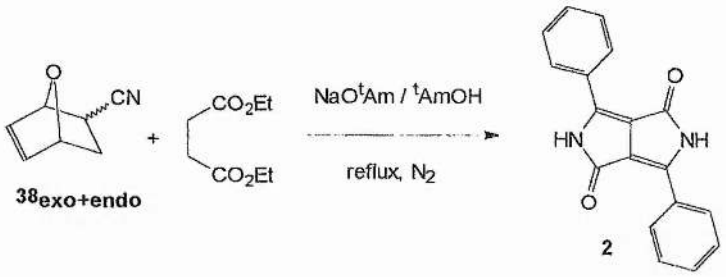
To pre-dried *t*-amyl alcohol (25 ml) was added sodium (0.46 g, 0.0200 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved, then cooled to 40 °C. The lactam ester **35** (1.57 g, 0.0068 mol) then the nitrile **38** (0.94 g, 0.0078 mol) were added and the mixture was stirred at 25 °C for 3.5 days. A bright red precipitate gradually formed. The mixture was then added to an ice-cooled mixture of methanol and concentrated hydrochloric acid (2 ml). The red precipitate was filtered off, washed with methanol and dried *in vacuo*. Yield 1.0 g (48%). All other data consistent with an authentic sample of **2**.



Reaction of the nitrile mixture 39 with the lactam ester 35

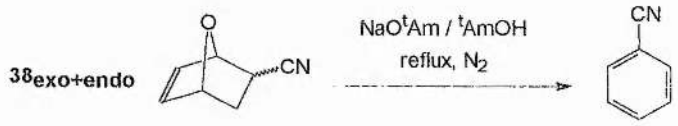
To pre-dried *t*-amyl alcohol (125 ml) was added sodium (1.38 g, 60 mmol) with stirring under nitrogen, and the mixture heated to reflux (105-110 °C) until all the sodium dissolved and then cooled to 65-70 °C. The lactam ester **35** (4.04 g, 17.5 mmol) then the nitrile **39** (3.00 g, 22.2 mmol) were added and the mixture stirred at 85-90 °C for 3.5 h. The mixture was then added to an ice-cooled mixture of methanol (50 ml) and concentrated hydrochloric acid (6 ml). The bright red precipitate was filtered off, washed with methanol and dried *in vacuo*. Yield 2.42 g (46 %). For the mixture of isomers, δ_H (200 MHz, DMSO-d_6) 2.28 and 2.38 (s, 2 x

CH_3), 7.34-8.51 (m, Ar- H), 10.90-11.30 (4H, m, NH, removed upon D_2O exchange). *m/z* 302 ($M^{+\cdot}$, 100%), 288 (7), 91 (49).



Reaction of nitrile 38 with diethyl succinate

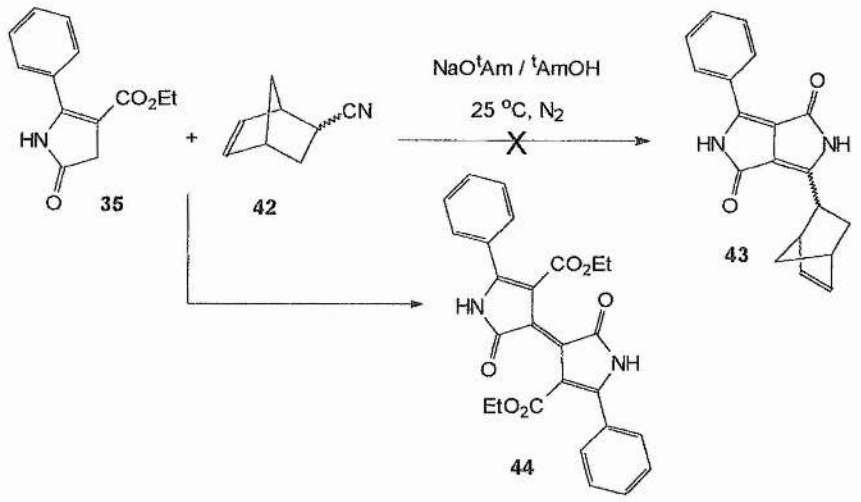
To pre-dried *t*-amyl alcohol (50 ml) was added sodium (1.12 g, 0.0487 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. A mixture of the nitrile **38** (1.96 g, 0.0162 mol) and diethyl succinate (2.82 g, 0.0162 mol) was then added portionwise over 1 h and stirring continued for 2 h at reflux, then for 16 h at 25 °C. The mixture was added to an ice-cooled mixture of methanol (30 ml) and concentrated hydrochloric acid (4.5 ml). The red precipitate was filtered off, washed with methanol and dried *in vacuo*. Yield 2.62 g (> 100 %): all data consistent with an authentic sample of **2** and elemental analysis suggested trace inorganic impurity The filtrate was concentrated and found to have the pungent odour of benzonitrile; GC and ^{1}H NMR analysis confirmed the presence of the latter.



Reaction of the nitrile 38 with sodium *t*-amyloxide

To pre-dried *t*-amyl alcohol (50 ml) was added sodium (0.56 g, 0.0244 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. Nitrile **38** (1.0 g, 0.0083 mol) was then added to the solution at reflux. A white precipitate quickly formed. Stirring was continued at reflux for 4 h, then the mixture was acidified with concentrated hydrochloric acid (3 ml). The light yellow solution containing a white precipitate was concentrated, washed with water (upon which the precipitate dissolved), extracted with diethyl ether, dried and concentrated to give a small amount of white solid and a colourless oil (~50 mg) with

a pungent odour of benzonitrile. ^{1}H and ^{13}C NMR confirmed the presence of benzonitrile and a small amount of unreacted nitrile **38**.



Attempted reaction of the lactam ester 35 with nitrile 42

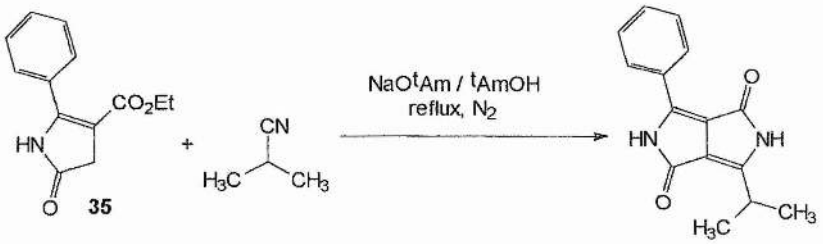
To pre-dried *t*-amyl alcohol (150 ml) was added sodium (3.55 g, 0.1544 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The solution was cooled to 25 °C then the lactam ester **35** (10.06 g, 0.0435 mol) and 5-norbornene-2-carbonitrile **42** (7.74 g, 0.0649 mol) were added. The mixture was stirred at 25 °C for 6 days then added to a mixture of water (100 ml) and methanol (5 ml) then acidified with concentrated hydrochloric acid (15 ml) dropwise. The organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel H eluted with petrol / ethyl acetate (2/1), then ethyl acetate and methanol yielded four fractions:

- fraction 1 (5.0 g) was a yellow oil, ^{1}H NMR ($CDCl_3$) and infra-red analysis spectral data showed predominantly unreacted 5-norbornene-2-carbonitrile **42** with a small amount of alkenic material with chemical shift δ_H 5.58 (dd, J 2.2 and 5.7).

- fraction 2 (0.38 g) was a beige solid, *m* = 231 (M^+, 13 %), 158, 105, 71 and ^{1}H NMR consistent with lactam ester **35**.

- fraction 3 (4.56 g) was a brown solid, ^{1}H NMR and mass spectrum consistent with unreacted lactam ester **35**.

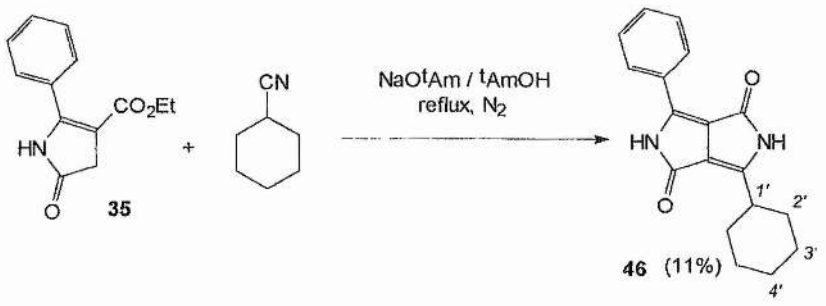
- fraction 4 (3.88 g) was a purple solid, ^{1}H NMR (DMSO-d_6) data consistent with the structure **44**, the product of oxidative dimerisation. δ_H (200 MHz, DMSO-d_6) 1.06 (6H, t, J 7.1, 2 x OCH_2CH_3), 3.97 (4H, q, 2 x OCH_2CH_3), 7.42-7.45 (6H, m, Ar-H), 7.54-7.59 (4H, m, Ar-H), 10.65 (2H, br. s, NH). *m/z* 458 ($M^{+\cdot}$, 5 %), 341, 231, 105, 71.



45 (31%)

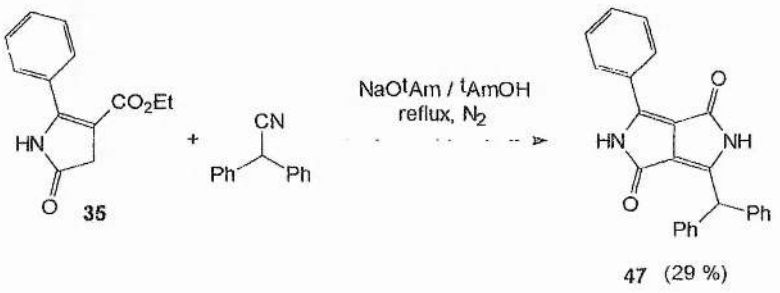
3-Isopropyl-6-phenyl-DPP 45

To pre-dried *t*-amyl alcohol (30 ml) was added sodium (0.63g, 0.0274 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The solution was cooled to 80-90 °C, then the lactam ester **35** (2.0 g, 0.0086 mol) and isobutyronitrile (0.69 g, 0.0110 mol) were added and stirring continued for 1 h. The mixture was then heated to reflux for 2 h, further isobutyronitrile (0.67 g, 0.0097 mol) was added and stirring continued for 1.5h at reflux. After stirring for a further 15 h at 25 °C, the mixture was added to an ice-cooled mixture of methanol (20 ml), water (30 ml) and concentrated hydrochloric acid (3 ml). The yellow precipitate was filtered off, washed with methanol and water then dried *in vacuo*. Yield 0.65 g (31%), m.p. 306-307 °C. (Found: C, 71.1; H, 5.5; N, 10.6. $C_{15}H_{14}N_2O_2$ requires C, 70.9, H, 5.6; N, 11.0 %). ν/cm^{-1} 3140 (N-H), 1654 (C=O). δ_H (DMSO-d_6) 1.28 (3H, s, $CHCH_3$), 1.30 (3H, s, $CHCH_3$), 2.91 (1H, septet, J 6.9, $CHCH_3$), 7.51-7.53 (3H, m, *m*- *p*- Ar-H), 8.33-8.37 (2H, m, *o*- Ar-H), 10.59 and 10.85 (each 1H, s, NH, reduced on D_2O exchange). λ_{max} / nm (DMSO) 437(sh) (ε 12872).



3-Cyclohexyl-6-phenyl-DPP 46

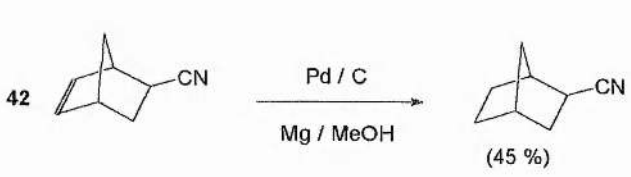
To pre-dried *t*-amyl alcohol (40 ml) was added sodium (0.64g, 0.0278 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The mixture was cooled to 80-90 °C then the lactam ester **35** (2.0 g, 0.0086 mol) and cyclohexanecarbonitrile (1.16 g, 0.0106 mol) were added. The mixture was heated to reflux for 1 h, then further cyclohexanecarbonitrile (1.20 g, 0.0110 mol) was added and stirring continued at reflux for 2 h. The mixture was stirred for 14 h at 25 °C and was then added dropwise to an ice-cooled mixture of methanol (10 ml), water (10 ml) and concentrated hydrochloric acid (2.5 ml). The yellow precipitate was filtered off, washed with methanol and water then dried *in vacuo* at 100 °C. Yield 0.28 g (11%). Sublimes without melting at >400°C. (Found: C, 72.6; H, 6.0; N, 9.1. $C_{18}H_{18}N_2O_2$ requires C, 73.5, H, 6.2; N, 9.5 %). ν/cm^{-1} 3143 (N-H), 1648 (C=O), 1609. δ_H (DMSO-d_6) 1.10-1.31 (4H, m, cyclohexyl H), 1.65-1.89 (6H, m, cyclohexyl H), 2.50-2.65 (1H, m, H-1'), 7.43-7.56 (3H, m, *m-/p-* Ar-H), 8.34-8.37 (2H, m, *o-* Ar-H), 10.56 and 10.87 (each 1H, s, NH, reduced on D_2O exchange). λ_{max} / nm (DMSO) 439 (ε 16006), 460 (15350).



3-Diphenylmethyl-6-phenyl-DPP 47

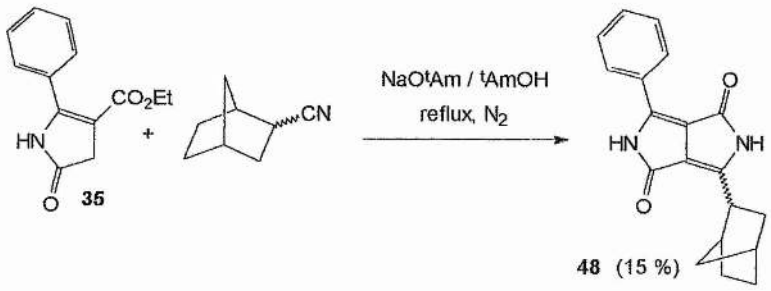
To pre-dried *t*-amyl alcohol (40 ml) was added sodium (0.69g, 30.0 mmol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the

sodium dissolved. The mixture was cooled to 80-90 °C then the lactam ester **35** (2.01 g, 8.7 mmol) and diphenylacetonitrile (1.73 g, 9.0 mmol) were added. The mixture was heated to reflux for 3.5 h, stirred at 25 °C for 18 h then added dropwise to an ice-cooled mixture of methanol (20 ml), water (10 ml) and concentrated hydrochloric acid (3.5 ml). The yellow precipitate was filtered off, washed with methanol and water then dried *in vacuo* at 100 °C. Yield 0.95 g (29 %), m.p. 295-296 °C. (Found: C, 79.0; H, 4.6; N, 7.4. $C_{25}H_{18}N_2O_2$ requires C, 79.4, H, 4.8; N, 7.4 %). ν/cm^{-1} 3138 (N-H), 1679 (C=O), 1645. δ_H (DMSO-d_6) 5.58 (1H, s, Ar-CH), 7.27-7.40 (10H, m, CH-Ar-*H*), 7.53-7.55 (3H, m, *m*-,*p*- Ar-H), 8.36-8.38 (2H, m, *o*- Ar-H), 10.82 and 10.95 (each 1H, s, NH, reduced on D_2O exchange). λ_{max} / nm (DMSO) 443 (ε 17940), 466 (17284).



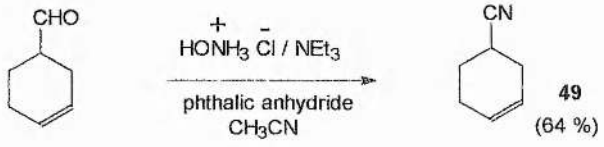
Norbornane-2-carbonitrile

To a mixture of 5-norbornene-2-carbonitrile **42** (5.0 g, 0.0420 mol), methanol (100 ml) and 5 % palladium on charcoal (0.4 g) was added magnesium (5.17 g, 0.2127 mol). After a brief induction period, the reaction proceeded with brisk evolution of gas until all the magnesium dissolved. The mixture was then added to ice-cooled 30 % hydrochloric acid, extracted with an ethyl acetate/diethyl ether mixture, dried (Na_2SO_4) then concentrated. Kugelrohr distillation (90-100 °C / 1 mmHg) yielded a colourless oil (2.30 g, 45 %) which solidified upon standing (lit.,[74] 62 °C / 7 Torr). δ_H 1.19-2.03 (8H, m), 2.34-2.72 (3H, m).



3-Norbornyl-6-phenyl-DPP 48

To pre-dried *t*-amyl alcohol (30 ml) was added sodium (1.16 g, 0.0504 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (3.18 g, 0.0138 mol) then 2-norbornanecarbonitrile (2.00 g, 0.0165 mol) were added and an orange-red solution gradually developed. Heating was continued for 3 h, then the solution was added to a mixture of water (100 ml) and concentrated hydrochloric acid (5 ml). The yellow-brown precipitate was filtered off, washed with water then methanol and dried *in vacuo*. Yield 0.62 g (15%), sublimed above 400 °C. Elemental analysis shows small impurity (Found: C, 73.3 ; H, 5.8 ; N, 8.6 . $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9 ; N, 9.1 %). δ_H (DMSO-d_6) 1.14-1.31 (3H, m, norbornyl H), 1.42-1.60 (4H, m, norbornyl H), 2.28-2.29 (2H, m, norbornyl H), 2.58-2.61 (2H, m, norbornyl H), 7.44-7.51 (3H, m, *m-/p-* Ar-H), 8.36-8.37 (2H, m, *o-* Ar-H), 10.60 and 10.91 (each 1H, s, NH, reduced on D_2O exchange). λ_{max} / nm (DMSO) 430 (ε 17381), 449 (17371).

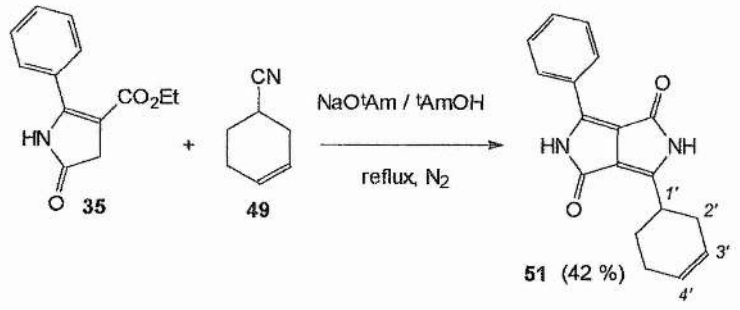


Cyclohexene-3-carbonitrile 49

The literature method[82] was adapted as follows:

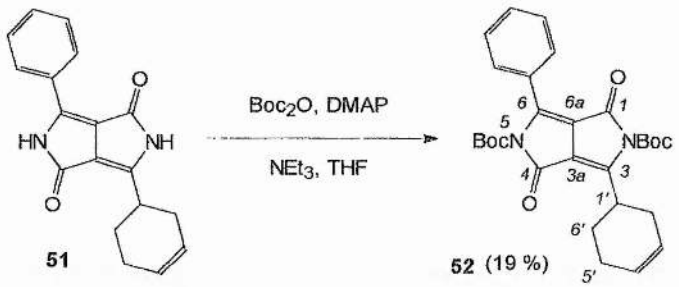
To a stirred mixture of 1,2,4,6-tetrahydrobenzaldehyde (20.50 g, 0.1861 mol), hydroxylamine hydrochloride (19.80 g, 0.285 mol) and pre-dried acetonitrile (160 ml) under nitrogen was added triethylamine (20.70 g, 0.205 mol). The mixture was heated to reflux (80 °C). Phthalic anhydride (30.41 g, 0.205 mol) was then added portionwise during 3h and heating was continued for a further 2 h. The mixture was

stirred at 25 °C for 16 h then concentrated, extracted with dichloromethane, the white precipitate filtered and the combined filtrates washed with 10 % aqueous ammonia, dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel H eluted with dichloromethane yielded a colourless oil (12.74 g, 64 %). ν/cm^{-1} 2240 (C≡N), 1654 (C=C). δ_H (200 MHz) 1.86-2.30 (4H, m, 2 x CH_2), 2.31-2.45 (2H, m, CH_2), 2.76-2.89 (1H, m, *CH*CN), 5.59-5.79 (2H, m, *HC*=*CH*).



3-Cyclohexenyl-6-phenyl-DPP 51

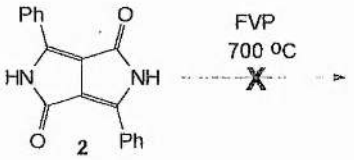
To pre-dried *t*-amyl alcohol (35 ml) was added sodium (1.76 g, 0.0779 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (5.02 g, 0.0217 mol) then cyclohexene-3-carbonitrile **49** (2.33 g, 0.0217 mol) were added and heating to reflux continued for 6.5 h. The mixture was added to crushed ice and concentrated hydrochloric acid (5 ml), acidified then the yellow-brown precipitate filtered off, washed with water then methanol and dried *in vacuo*. Yield 2.66 g (42 %), m.p. 358-360 °C with colour change to orange-red. (Found: C, 73.1; H, 5.3; N, 9.3. $C_{18}H_{16}N_2O_2$ requires C, 74.0; H, 5.5; N, 9.6 %). δ_H (DMSO-d_6) 1.82-2.89 (7H, m, cyclohexenyl H-1' and 3 x CH_2), 5.65-5.78 (2H, m, H-3' and -4'), 7.50-7.53 (3H, m, *m*-/*p*- Ar-H), 8.34-8.36 (2H, m, *o*-Ar-H), 10.61 (1H, s, NH), 10.88 (1H, s, NH).



51 52 (19 %)

2,5-Bis-*t*-butoxycarbonyl-3-cyclohexenyl-6-phenyl-DPP 52

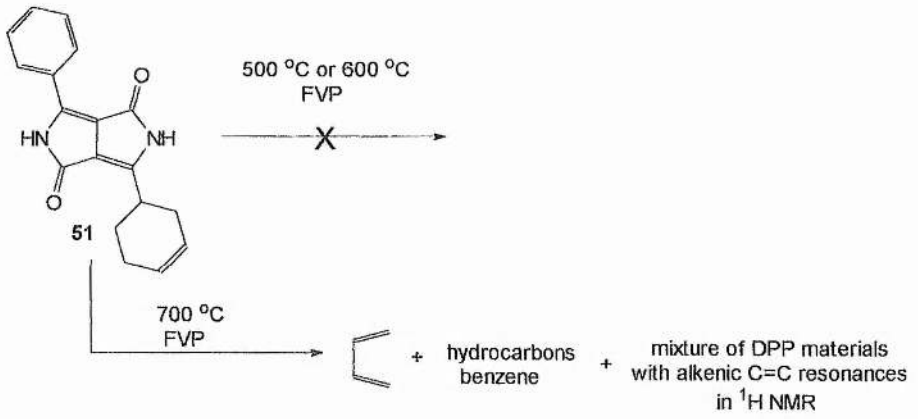
A mixture of 3-cyclohexenyl-6-phenyl-DPP **51** (0.39 g, 13 mmol), DMAP (0.02 g, 0.16 mmol), Boc_2O (1.02 g, 47 mmol), triethylamine (0.42 g, 42 mmol) and tetrahydrofuran (30 ml) was stirred with exclusion of moisture for 8 h, then concentrated. The residue was mixed with methanol (2 ml), the mixture filtered and the fluorescent yellow residue then washed with methanol and dried *in vacuo*. Yield 0.12 g (19 %), decomposed without melting. (Found: C, 68.7; H, 6.8; N, 5.6. $C_{28}H_{32}N_2O_6$ requires C, 68.3; H, 6.6; N, 5.7 %). Single crystals suitable for X-ray analysis were prepared via recrystallisation from an ethanol-tetrahydrofuran mixture. δ_H 1.38 [9H, s, OC(CH_3)$_3$], 1.58 [9H, s, OC(CH_3)$_3$], 1.98-2.10 (1H, m, CH_2), 2.19-2.33 (4H, m, 2 x CH_2), 2.73-2.83 (1H, m, CH_2), 3.23-3.32 (1H, m, *H*CCH_2), 5.71-5.82 (2H, m, *H*C=C*H*), 7.30-7.48 (3H, m, *m-/p-* Ar-H), 7.67-7.76 (2H, m, *o-* Ar-H). δ_C (50.3 MHz) 25.11, 26.42, 27.38, 27.81, 29.08 and 34.79 [2 x OC(CH_3)$_3$, C-1', -2', -5' and -6'], 85.04 and 85.38 [OC(CH$_3$)$_3$], 110.40 and 111.26 (C-3 and -6), 125.33, 126.37, 128.08, 128.28, 128.38 and 131.13 (Ar-C, C-3' and -4'), 144.89 (C-3a), 148.06 and 148.49 (C-1 and -4), 156.97 (C-6a), 158.81 and 159.16 [C=O(CH$_3$)$_3$]. See Appendix 1 (page 145) for details of X-ray structure analysis.



2

Flash vacuum pyrolysis of diphenyl-DPP 2

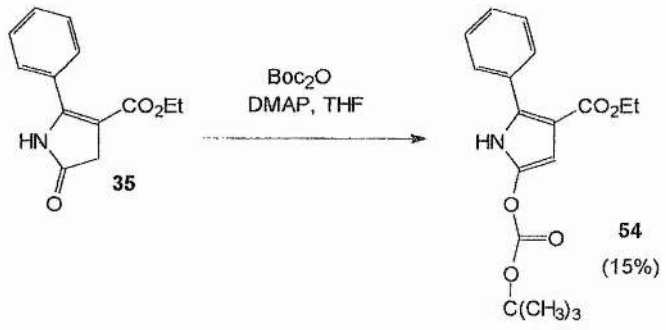
3,6-Diphenyl-DPP **2** was heated under flash vacuum pyrolysis conditions to a temperature of 700 °C under a pressure of $7x10^{-2}$ Torr. A red solid was collected at the furnace outlet. The infra-red spectrum was identical with an authentic sample of diphenyl-DPP **2**.



Flash vacuum pyrolysis of DPP 51

The DPP product **51** was heated under flash vacuum pyrolysis conditions, with a pressure of $8x10^{-3}$ Torr and an inlet temperature to the furnace of 300-330 °C. In each case a 100 mg sample (± 10 mg) was used. The furnace temperature and results were as follows:

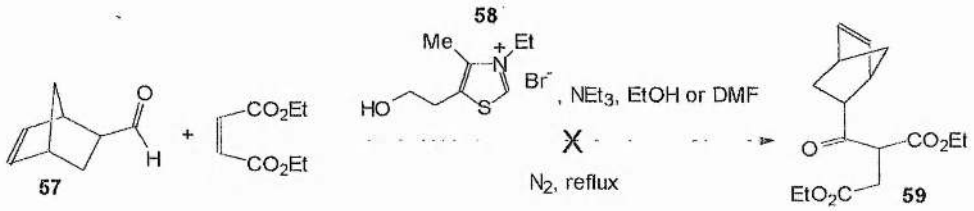
temperature	products
500 and 600 °C	1. A yellow-orange solid was collected at the furnace outlet. ^{1}H NMR was consistent with starting material **51**.
	2. $CDCl_3$ was used to rinse out the trap, but no products were detected by ^{1}H NMR other than a trace amount of benzene.
700 °C	1. A fluorescent orange solid was collected at the furnace outlet. δ_H (DMSO-d_6) 5.74-5.94 (m, alkenic H), 6.61-6.65 (m, alkenic H), 7.27-7.48 (m, Ar-H), 7.56-7.83 (m, Ar-H), 8.32-8.60 (m, Ar-H), 10.63, 10.93, 10.97, 11.18, 11.19 and 11.36 (s, NH).
	2. $CDCl_3$ was used to rinse out the trap: ^{1}H NMR of this solution showed butadiene and benzene. δ_H 5.07-5.24 (4H, m, CH_2 CH), 6.23-6.40 (2H, m, CH_2 CH), 7.34 (trace amount, s, benzene),



Ethyl 5-*t*-butoxycarbonyl-2-phenylpyrrole-3-carboxylate 54

A mixture of the lactam ester **35** (0.37 g, 0.0016 mol), DMAP (0.05 g, 0.4 mmol), Boc_2O (0.39 g, 1.8 mmol) and tetrahydrofuran (25 ml) was stirred at 25 °C for 24 h and the solution then concentrated to give a red-yellow oil. Flash chromatography on silica gel H and eluted with petrol / ethyl acetate (2:1) yielded unreacted lactam ester **35** and a white solid product which was recrystallised from 70 % aqueous ethanol and dried *in vacuo*. Yield 0.08 g (15 %), m.p. 125-126 °C. (Found: C, 65.3; H, 6.5; N, 4.2. $C_{18}H_{21}NO_5$ requires C, 65.3; H, 6.4; N, 4.2 %). δ_H 1.25 (3H, t, J 7.1, OCH_2CH_3), 1.57 [9H, s, $C(CH_3)_3$], 4.21 (2H, q, OCH_2CH_3), 6.30 (1H, s, pyrrole H), 7.35-7.43 (3H, m, *m*-,*p*- Ar-H), 7.58-7.61 (2H, m, *o*- Ar-H), 8.74 (1H, br.s, NH). See Appendix 2 (page 150) for details of X-ray structure analysis.

6.3 Experimental for Chapter 3

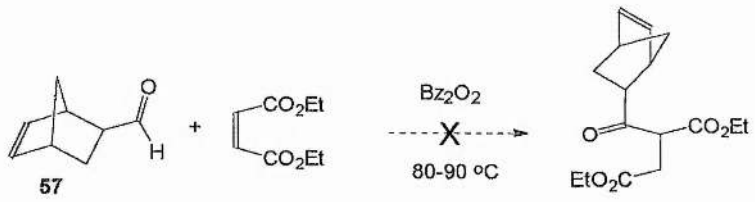


Attempted acylation of diethyl maleate via the Stetter reaction

(a) A mixture of redistilled 5-norbornene-2-carboxaldehyde **57** (2.52 g, 0.0206 mol), diethyl maleate (2.94 g, 0.0171 mol), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **58** (0.26 g, 0.0010 mol), triethylamine (0.65 g, 0.0064 mol) and absolute ethanol (10 ml) was stirred at reflux (60-70 °C) under

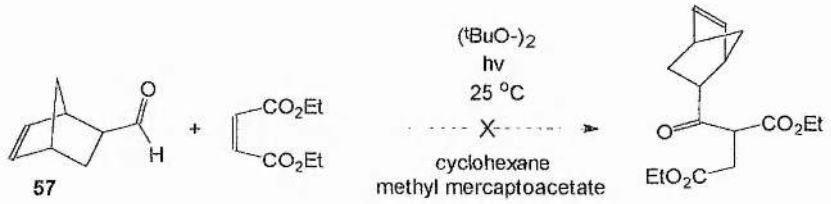
nitrogen for 30 h. ^{1}H NMR and tlc of the crude reaction mixture confirmed that only unreacted starting materials were present.

(b) A mixture of redistilled 5-norbornene-2-carboxaldehyde **57** (1.29 g, 10.6 mmol), diethyl maleate (1.82 g, 10.5 mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **58** (0.13 g, 0.5 mmol) and triethylamine (0.53 g, 52 mmol) was heated to 60 °C under nitrogen for 15 h. ^{1}H NMR indicated that no reaction had occurred. Further catalyst **58** (0.2 g, 0.8 mmol) and dry DMF (2ml) were then added and heating to 70 °C continued for 4.5 h. ^{1}H NMR of the crude mixture confirmed that only unreacted starting materials were present.



Attempted acylation of diethyl maleate via free-radical addition

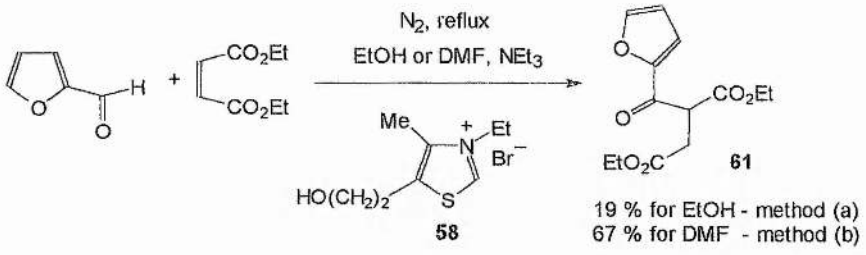
A mixture of 5-norbornene-2-carboxaldehyde **57** (2.55 g, 0.0209 mol), diethyl maleate (1.39 g, 0.0081 mol) and dibenzoyl peroxide (0.1 g, 0.0004 mol) was heated at 80-90 °C for 4 days. ^{1}H NMR of the crude mixture confirmed that only unreacted starting materials were present.



Attempted acylation of diethyl maleate via free-radical addition

A mixture of 5-norbornene-2-carboxaldehyde **57** (0.98 g, 0.0080 mol), diethyl maleate (1.39 g, 0.0081 mol), cyclohexane (2 ml) and *t*-butyl peroxide (0.06 g, 0.4 mmol) was degassed with nitrogen for 30 min and then was irradiated with a UV lamp for 3.5 h in a quartz tube. 'H NMR showed only unreacted starting materials. Further *t*-butyl peroxide (0.05 g, 0.3 mmol) and methyl mercaptoacetate (1 drop) were added, the mixture was degassed with nitrogen during 30 min and then was

irradiated with a UV lamp for 4 h. ^{1}H NMR again showed only unreacted starting materials.

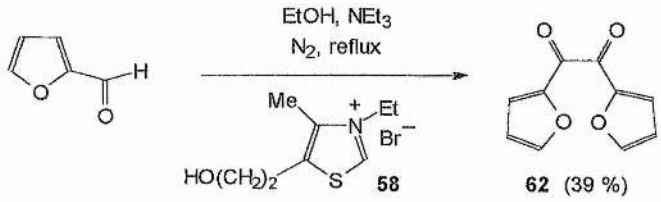


Diethyl 2-furoylsuccinate 61

Method (a) A mixture of diethyl maleate (8.64 g, 50.2 mmol), triethylamine (1.92 g, 19 mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **58** (0.76 g, 3 mmol) was heated to reflux (80-85 °C) under nitrogen then furfural (5.77 g, 60 mmol) was added portionwise during 5 h. Stirring was continued at 25 °C for 60 h, then at reflux for a further 4 h. The mixture was added to a mixture of water and dilute hydrochloric acid, then the acidified mixture was extracted with ether and a white precipitate was filtered off. The organic filtrates were collected and washed with sodium hydrogen carbonate solution then water and dried (Na_2SO_4). Distillation (Kugelrohr) yielded a colourless fraction (3.99 g, 100-140 °C / 0.5 mmHg) identified as unreacted diethyl maleate and furfural, together with an orange-yellow fraction (3.28 g, 200-205 °C / 0.5 mmHg). ^{1}H NMR showed that this final fraction was 80 % product **61**. Yield 2.62 g, 19 %. No furil side-product was identified from ^{1}H NMR.

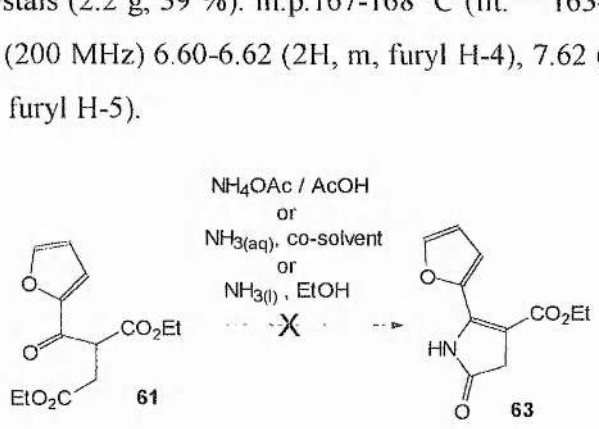
Method (b) To a mixture of diethyl maleate (11.42 g, 0.0663 mol), triethylamine (1.92 g, 0.0190 mol) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **58** (0.80 g, 0.0032 mol) heated at 90-100 °C under nitrogen was added freshly distilled furfural (3.26 g, 0.0339 mol) portionwise over 2 h. Dry *N,N*-dimethylformamide (4 ml) was then added, heating continued at 80 °C for 4 h, and thereafter stirring for 15 h at 25 °C. The mixture was reheated to 80-90 °C for 8 h, then added to a mixture of water (20 ml) and 2M hydrochloric acid (30 ml), extracted with dichloromethane, the extract washed with sodium hydrogen carbonate solution, then water, and dried (Na_2SO_4). The extracts were then concentrated and distilled (Kugelrohr) to give recovered diethyl maleate (5.43 g) and a brown residue. Flash chromatography on silica gel H eluted with petrol / ethyl acetate (2:1) yielded a light orange-yellow oil (6.12 g, 67%). δ_H 1.19 (3H, t, J 7.1, OCH_2CH_3), 1.23 (3H, t, OCH_2CH_3), 2.99 (1H,

dd, $J_{vicinal}$ 7.0 and $J_{geminal}$ 17.4, CH_2CO_2Et), 3.07 (1H, dd, CH_2CO_2Et), 4.14 (2H, q, OCH_2CH_3), 4.16 (2H, q, OCH_2CH_3), 4.65 (1H, t, J 7.2, $CHCO_2Et$), 6.59 (1H, dd, J 1.7 and 3.6, furyl H-4), 7.36-7.37 (1H, m, furyl H-3), 7.65-7.66 (1H, m, furyl H-5). δ_C (50.3 MHz) 13.89 (OCH_2CH_3), 14.03 (OCH_2CH_3), 32.6 (CH_2CO_2Et), 49.79 ($CHCO_2Et$), 61.0 (OCH_2CH_3), 61.77 (OCH_2CH_3), 112.66 (furyl C-4), 118.95 (furyl C-3), 147.18 (furyl C-5), 151.70 (furyl C-2), 168.40 ($COCH_2CH_3$), 171.04 ($COCH_2CH_3$), 182.54 (furyl-CO).



Furil 62

A mixture of triethylamine (0.95 g, 9.4 mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **58** (0.41 g, 1.6 mmol), furfural (2.88 g, 30 mmol) and ethanol (13 ml) was heated to reflux with the exclusion of moisture for 3 h, then at 25 °C for 65 h. The mixture was added to ice, acidified with dilute hydrochloric acid and the yellow precipitate was then filtered off. Recrystallisation from propan-2-ol yielded yellow crystals (2.2 g, 39 %). m.p.167-168 °C (lit.[107] 163-165 °C and lit for furoin 133 °C). δ_H (200 MHz) 6.60-6.62 (2H, m, furyl H-4), 7.62 (2H, d, J 3.7, furyl H-3), 7.76 (2H, m, furyl H-5).



Attempted synthesis of the furyl lactam ester 63 from the ring closure of 61

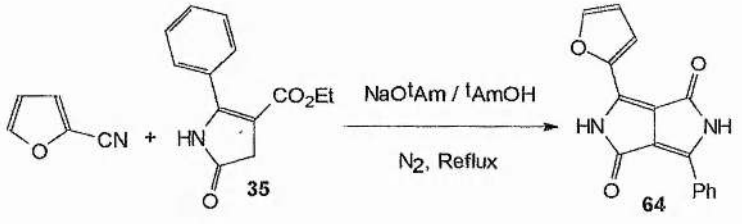
The derivative **61** was subjected to reaction with various ammonia equivalents as follows:

(a) A solution of diethyl 2-furoylsuccinate **61** (0.5g, 19 mmol), ammonium acetate (1.52 g, 197 mmol) and acetic acid (5 ml) was heated to reflux under nitrogen for

7.5 h and then was added to ice-water. An intractable black solid was precipitated (0.25 g).

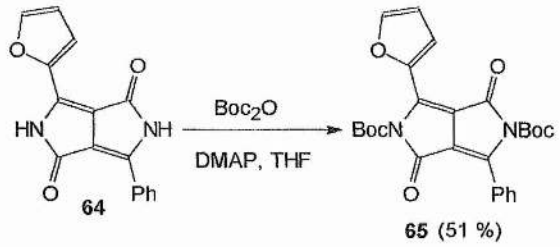
(b) To a mixture of diethyl 2-furoylsuccinate **61** (0.1 g, 0.4 mmol) and ethanol (2 ml) was added concentrated aqueous ammonia (2.5ml). The mixture was stirred at 25 °C for 72 h and then was concentrated to yield a brown oil. ^{1}H NMR confirmed only unreacted starting material.

(c) To diethyl 2-furoylsuccinate **61** (0.54 g, 20 mmol) was added a mixture of ethanol (40 ml) and liquid ammonia (9.7 g). The mixture was stirred at 25 °C for 4 days and was then concentrated to yield a brown oil. ^{1}H NMR confirmed only unreacted starting materials.



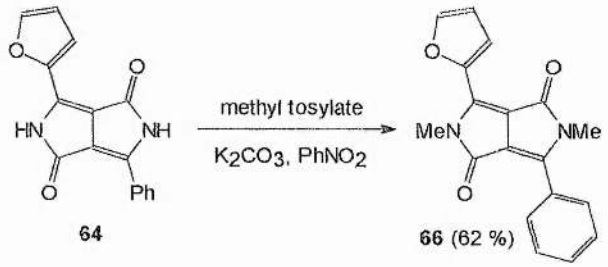
2-(2-Furyl)-6-phenyl-DPP 64

To pre-dried *t*-amyl alcohol (30 ml) was added sodium (0.39 g, 0.0170 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (1.24 g, 0.0054 mol) was then added. 2-Furonitrile (0.54 g, 0.0058 mol) was then added portionwise over 25 min, during which time a red-purple precipitate gradually formed. Heating to reflux was continued for 3 h, then for 16 h at 25 °C. The mixture was then added to an ice-cooled mixture of methanol (40 ml) and concentrated hydrochloric acid (2.5 ml) then the red precipitate was filtered off, washed with methanol and water then dried *in vacuo*. Yield 1.05 g (70 %), m.p. >400 °C. (Found: C, 69.1; H, 3.5; N, 9.8. $C_{16}H_{10}N_2O_3$ requires C, 69.1, H, 3.6; N, 10.1 %). δ_H (DMSO-d_6) 6.85 (1H, dd, J 1.8 and 3.6, furyl H-4), 7.52-7.56 (3H, m, *m*- *p*- Ar-H), 7.75 (1H, d, furyl H-3), 8.08 (1H, d, furyl H-5), 8.40-8.45 (2H, m, *o*- Ar-H), 11.27 (1H, s, NH, reduced on D_2O exchange), 11.32 (1H, s, NH, reduced on D_2O exchange). m/z 278 (M^+, 100%).



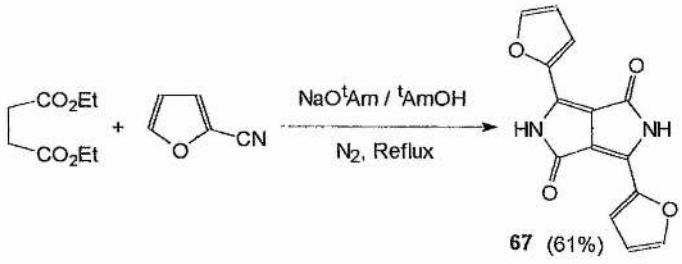
2,5-Bis-*t*-butoxycarbonyl-2-(2-furyl)-6-phenyl-DPP 65

A mixture of 2-(2-furyl)-6-phenyl-DPP **64** (0.25 g, 0.9 mmol), Boc_2O (0.59 g, 2.7 mmol), DMAP (0.03 g, 0.2 mmol) and tetrahydrofuran (20 ml) were stirred at 25 °C for 19 h. The reaction mixture was concentrated, the residue mixed with methanol (1 ml), filtered and washed with methanol (1 ml) then the bright orange solid dried *in vacuo*. Yield 0.22 g (51%). The product decomposed without melting. λ_{max} /nm (acetonitrile) 454.8 (ε 20842). δ_H 1.39 [9H, s, $OC(CH_3)_3$], 1.57 [9H, s, $OC(CH_3)_3$], 6.70 (1H, dd, J 1.9 and 3.6, furyl H-4), 7.45-7.51 (3H, m, *m-/p-* Ar-H), 7.62 (1H, d, furyl H-3), 7.70-7.75 (2H, m, *o-* Ar-H), 8.01 (1H, d, furyl H-5).



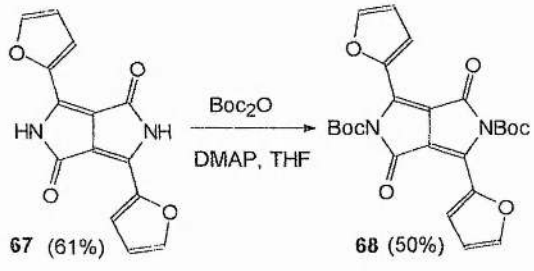
2,5-Dimethyl-3-(2-furyl)-6-phenyl-DPP 66

A mixture of 3-(2-furyl)-6-phenyl-DPP **64** (1.76 g, 0.0063 mol), potassium carbonate (1.76 g, 0.0127 mol), nitrobenzene (50 ml) and methyl tosylate (3.06 g, 0.0164 mol) was stirred at 150 °C for 3.5 h, further methyl tosylate (2.36 g, 0.0127 mol) was added and heating continued for 2.5 h. After stirring for a further 15 h at 25 °C, the mixture was then added to water, extracted with dichloromethane, dried (Na_2SO_4), concentrated and dried *in vacuo* at 100 °C. Recrystallisation from IPA-tetrahydrofuran yielded red-orange crystals. Yield 1.19 g, 62 %, m.p. 193-194.5 °C. (Found: C, 70.9; H, 4.6; N, 9.0 % $C_{18}H_{14}NO_3$ requires C, 70.6, H, 4.6; N, 9.2 %). δ_H 3.40 (1H, s, NCH_3), 3.58 (1H, s, NCH_3), 6.72 (1H, dd, J 1.6 and 3.6, furyl H-4), 7.47-7.57 (3H, m, *m-/p-* Ar-H), 7.68 (1H, d, furyl H-3), 7.88 (1H, dd, furyl H-5), 8.31 (2H, d, *o-* Ar-H). See Appendix 3 (page 156) for details of X-ray structure analysis.



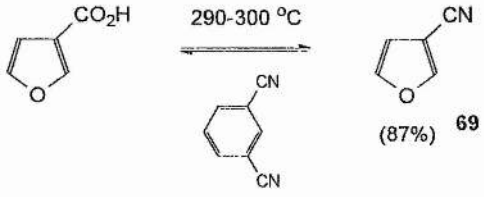
3,6-Di-(2-furyl)-DPP 67

To pre-dried *t*-amyl alcohol (10 ml) was added sodium (0.22 g, 0.0096 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. A mixture of 2-furonitrile (0.52 g, 0.0056 mol) and diethyl succinate (0.49 g, 0.0028 mol) was added portionwise over 1.5 h and stirring continued for 0.5 h at reflux. The mixture was added to an ice-cooled mixture of methanol (35 ml) and concentrated hydrochloric acid (1.5 ml); the dark purple precipitate was then filtered off, washed with methanol and water, then dried *in vacuo*. Yield 0.46 g (61%). (Found: C, 62.8; H, 2.8; N, 10.2. $C_{14}H_8N_2O_4$ requires C, 62.7; H, 3.0; N, 10.4%). δ_H (200 MHz, DMSO-d_6) 6.83 (2H, dd, J 1.8 and 3.6, furyl H-4), 7.67 (2H, d, furyl H-3), 8.05 (2H, d, furyl H-5), 11.19 (2H, s, NH). *m* / *z* 268 ($M^{+\cdot}$, 86%).



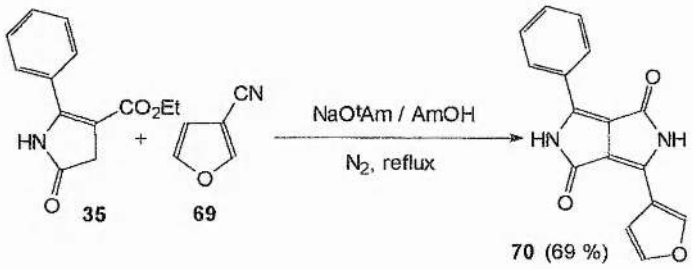
2-*t*-Butoxycarbonyl-3,6-(2-furyl)-DPP 68

A mixture of di-2-furyl DPP **67** (0.25 g, 0.9 mmol), Boc_2O (0.51 g, 2.3 mmol), DMAP (0.01 g, 0.08 mmol) and tetrahydrofuran (20 ml) was stirred at 25 °C for 19 h. The reaction mixture was concentrated, the residue then mixed with methanol (1 ml), filtered and washed with methanol (1 ml) then the dark orange solid was dried *in vacuo*. Yield 0.22 g (50%). The product decomposed without melting. λ_{max}/nm (acetonitrile) 476.1 (ε 28368), 500 (28308). δ_H (200MHz) 1.21 [18H, s, $OC(CH_3)_3$], 6.67 (2H, dd, J 1.3 and 3.6, furyl H-4), 7.61 (2H, d, furyl H-3), 7.93 (2H, d, furyl H-5).



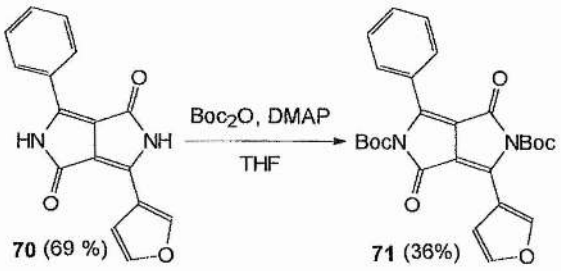
3-Furonitrile[100] **69**

A mixture of 3-furoic acid (3.61 g, 0.0322 mol) and 1,3-dicyanobenzene (10.74 g, 0.0838 mol) was heated gradually to 290-300 °C in a distillation apparatus fitted with a fractionating column. A colourless distillate [159-162 °C (lit. 151 °C)] was collected (2.47 g, 82 %); this solidified on standing, m.p. 23.5-24.5 °C. ν/cm^{-1} 2247 (C≡N). δ_H 6.64-6.65 (1H, m, furyl H-4), 7.51-7.52 (1H, m, furyl H-5), 7.97 (1H, d, J 0.8, furyl H-2).



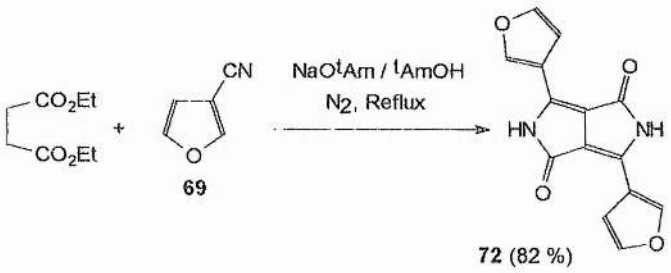
3-(3-Furyl)-6-phenyl-DPP 70

To pre-dried *t*-amyl alcohol (50 ml) was added sodium (1.64 g, 0.0713 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (5.30 g, 0.0229 mol) in *t*-amyl alcohol (25 ml) then 3-furonitrile **69** (2.14 g, 0.0230 mol) were added. Stirring was continued at reflux for 3 h, then at 25 °C for 24 h during which time a deep purple-red mixture gradually formed. The mixture was added dropwise to a mixture of methanol (90 ml) / concentrated hydrochloric acid (8 ml) at 0 °C and then the purple-red solid was filtered off, washed with methanol and water then dried *in vacuo*. Yield 4.39 g (69 %). This compound was not obtained completely pure (Found: C, 68.7; H, 3.8; N, 9.1. $C_{16}H_{10}N_2O_3$ requires C, 69.1; H, 3.6; N, 10.1 %) but gave the correct mass spectrum [*m* / *z* 278 ($M^{+\cdot}$, 6%), 221 (7), 181 (13), 105 (29), 91 (100), 77 (12), 55 (13)] and was converted for full characterisation into its di-boc derivative **71** (see below). ν/cm^{-1} 3138 (N-H), 1706, 1659, 1626 (C=O and N-H bending).



2,5-Bis-*t*-butoxycarbonyl-3-(3-furyl)-6-phenyl-DPP 71

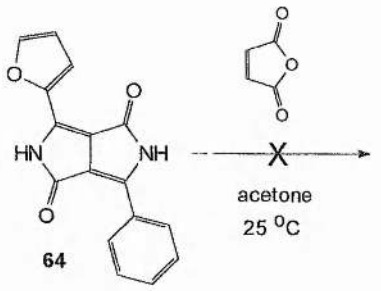
A mixture of 3-(3-furyl)-6-phenyl-DPP **70** (1.5g, 5.4 mmol), Boc_2O (2.67 g, 12.2 mmol), DMAP (0.13 g, 1.1 mmol), tetrahydrofuran (100 ml) and triethylamine (1.25 g, 12.4 mmol) was stirred at 25 °C for 3 h, further Boc_2O (1.22 g, 5.6 mmol) added, stirring continued for 86 h then further Boc_2O (1.26g, 5.8 mmol) added. After 7 h, the mixture was concentrated and a light yellow solid precipitated by addition of methanol (2ml) then filtered off and dried *in vacuo*. Yield 0.95 g (37 %). The product decomposed without melting. (Found: C, 64.3; H, 5.5; N, 5.6. $C_{26}H_{26}N_2O_7$ requires C, 64.3; H, 5.5; N, 5.85 %). δ_H 1.38 [9H, s, $OC(CH_3)_3$], 1.60 [9H, s, $OC(CH_3)_3$], 6.91 (1H, d, J 1.1, furyl H-4), 7.46-7.52 (3H, m, *m*-/*p*- Ar-H), 7.69-7.80 (3H, m, *o*- Ar-H and furyl H-5), 8.66 (1H, t, J 0.7, furyl H-2).



3,6-Di(3-furyl)-DPP 72

To pre-dried *t*-amyl alcohol (15 ml) was added sodium (0.20 g, 8.7 mmol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. The solution was cooled to 95 °C then a mixture of diethyl succinate (0.60 g, 3.4 mmol), 3-furonitrile **69** (0.65 g, 7.0 mmol) and *t*-amyl alcohol (1 ml) was then added during 10 min. upon which a dark purple precipitate slowly formed in a fluorescent yellow solution. Stirring was continued at 55-60 °C for 2 h then the mixture was added to an ice-cooled mixture of methanol (10 ml) and concentrated hydrochloric acid (0.5 ml). The purple precipitate was filtered off, washed with methanol then water and dried *in vacuo*. Yield 0.29 g (32 %).

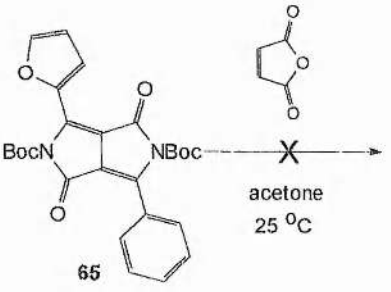
δ_H (DMSO-d_6) 7.34 (2H, m, furyl H-4), 7.87-7.88 (2H, m, furyl H-5), 8.63 (2H, m, furyl H-2), 11.07 (2H, s, NH). *m/z* 268.0473 ($M^{+\cdot}$ 100 %; $C_{14}H_8N_2O_4$ requires 268.0484).



64

Attempted Diels-Alder reaction of 2-(2-furyl)-6-phenyl-DPP 64 with maleic anhydride

A mixture of 2-furyl-6-phenyl-DPP **64** (0.1005 g, 0.2 mmol), maleic anhydride (0.2518 g, 2.5 mmol) and acetone (8 ml) was stirred at 25 °C for 16 h then at reflux (55-60 °C) for 8 h, but tlc showed only unreacted starting material. Zinc iodide (0.2 g) was added and stirring continued at 25 °C for 16 h. Tlc again showed only unreacted starting materials. The mixture was mixed with ethyl acetate, washed with 0.1 M sodium thiosulfate, the organic layer was separated, dried then concentrated. ^{1}H NMR confirmed that only unreacted starting materials were present.

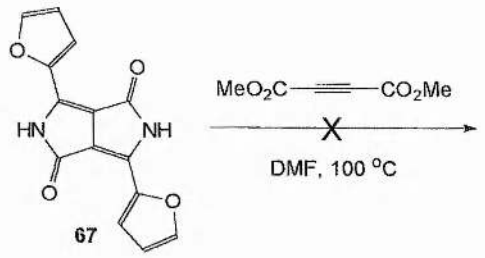


65

Attempted Diels-Alder reaction 2,5-bis-*t*-butoxycarbonyl-2-(2-furyl)-6-phenyl-DPP 65 with maleic anhydride

A mixture of 2,5-bis-*t*-butoxycarbonyl-2-(2-furyl)-6-phenyl-DPP **65** (0.1005 g, 0.2 mmol), maleic anhydride (0.2518 g, 2.5 mmol), acetone (8 ml) and zinc iodide (0.2 g) was heated to reflux (55-60 °C) for 8 h, then at 25 °C for 48 h. The mixture was mixed with ethyl acetate, washed with 0.1 M sodium thiosulfate, dried (Na_2SO_4)

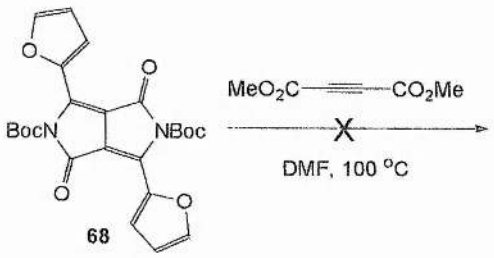
then concentrated. ^{1}H NMR confirmed that only unreacted starting materials were present in addition to 2-(2-furyl)-6-phenyl-DPP.



67

Attempted Diels-Alder reaction of 3,6-di-(2-furyl)-DPP 67 with DMAD

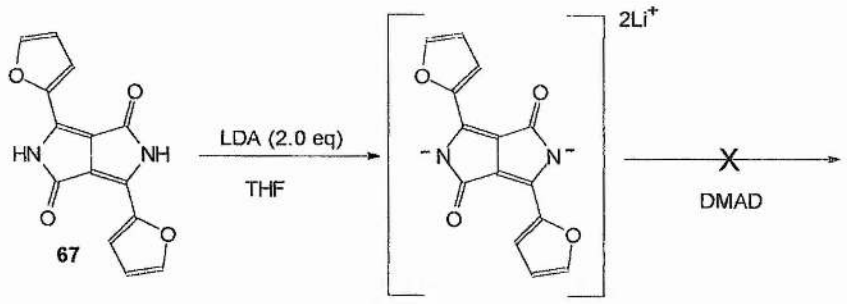
A mixture of 3,6-di-(2-furyl)-DPP **67** (0.05 g, 0.19 mmol), dimethyl acetylene dicarboxylate (0.16 g, 1.1 mmol) and DMF (5 ml) was heated to 95 °C for 24 h. Further DMAD (0.30 g, 2.1 mmol) was added and heating continued at 100 °C for 72 h then cooled and concentrated. ^{1}H NMR showed only unreacted starting materials.



68

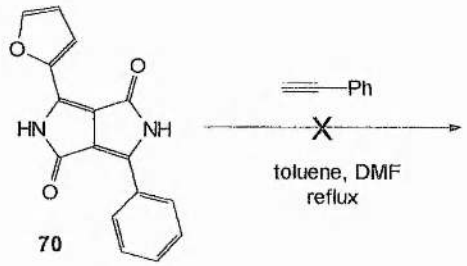
Attempted Diels-Alder reaction of DPP 68 with DMAD

A mixture of 2-*t*-butoxycarbonyl-3,6-(2-furyl)-DPP **68** (0.04 g, 0.008 mmol), dimethyl acetylene dicarboxylate (0.13 g, 0.09 mmol) and DMF (5 ml) were heated to 100 °C for 96 h, then cooled to 25 °C and concentrated. ^{1}H NMR showed only unreacted starting materials.



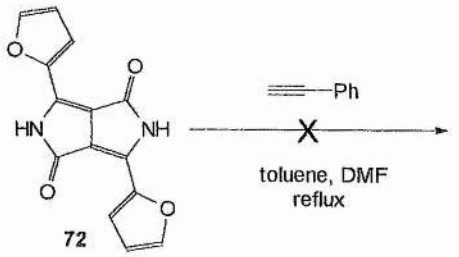
Attempted Diels-Alder reaction of di-2-furyl DPP 67 dianion with DMAD

To a flask charged with THF (20 ml) and diisopropylamine (0.55 g, 5.4 mmol) under nitrogen was added *n*-butyllithium (1.0 ml, 2.5 mmol, 1M solution in hexanes) then stirring continued for 1 h. The solution was cooled to -78 °C, a suspension of di-2-furyl-DPP **67** (0.30 g, 0.0011 mol) in tetrahydrofuran (20 ml) added dropwise and stirring was continued for 15 min. To the purple solution was then added dimethyl acetylene dicarboxylate (0.58 g, 0.0041 mol); stirring was continued for 1.5 h then the mixture was heated to reflux for 2 h. After stirring at 25 °C for 1 week saturated aqueous ammonium chloride solution was added, and the mixture extracted with diethyl ether, concentrated, then the purple residue was dried *in vacuo*. ^{1}H NMR confirmed only unreacted starting material.



Attempted Diels-Alder reaction of 3-(3-furyl)-6-phenyl-DPP 70

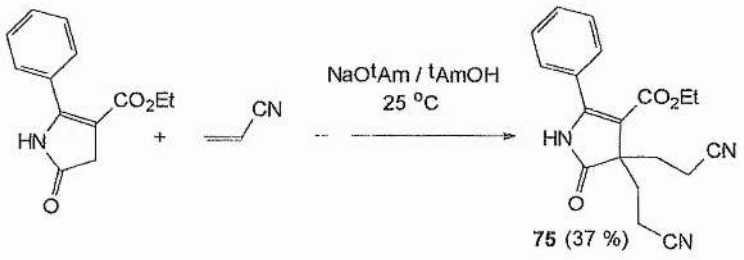
To a suspension of 3-(3-furyl)-6-phenyl-DPP **70** (0.15 g, 0.5 mmol) in toluene (10 ml) and DMF (10 ml) was added phenylacetylene (0.14 g, 1.4 mmol) then the mixture was heated to reflux for 5 h. Stirring was then continued at 25 °C for 2 days, zinc iodide (0.07 g, 0.21 mmol) was then added and stirring was continued for 12 days. ^{1}H NMR confirmed that only unreacted starting materials were present.



Attempted Diels-Alder reaction 3,6-di(3-furyl)-DPP 72

A mixture of 3,6-di(3-furyl)-DPP **72** (0.19 g, 0.7 mmol), phenylacetylene (0.32 g, 3.1 mmol), toluene (10 ml), DMF (10 ml) and zinc iodide (0.05 g) was heated to 100 °C for 39 h, then concentrated, ^{1}H NMR indicated only unreacted starting materials.

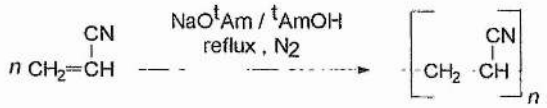
6.4 Experimental for Chapter 4



3,3-Bis-(cyanoethyl)-4-ethoxycarbonyl-5-phenyl-4-pyrrolin-2-one 75

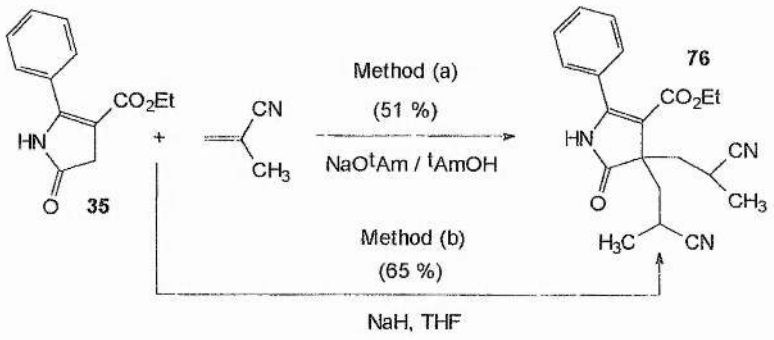
To pre-dried *t*-amyl alcohol (15 ml) was added sodium (0.23 g, 0.0100 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The mixture was cooled to 40 °C, then the lactam ester **35** (0.76 g, 0.0033 mol) and acrylonitrile (0.20 g, 0.0038 mol) were added. The mixture was stirred at 25 °C for 72 h and was then acidified to pH 5 with dilute hydrochloric acid (2M). The solution was concentrated to give a brown solid, then redissolved in dichloromethane, and washed with water then concentrated. Recrystallisation from propan-2-ol yielded beige crystals (0.24 g, 37 % based on acrylonitrile), m.p.160-161 °C. . (Found: C, 67.6; H, 5.5; N, 12.3. $C_{19}H_{19}N_3O_3$ requires C, 67.6; H, 5.7; N 12.5 %). ν/cm^{-1} 3249 (N-H), 2253 (C≡N), 1735 (C O), 1672 (C O). δ_H 1.12 (3H, t, J 7.1, OCH_2CH_3), 2.10-2.21 (3H, m, methylene CH_2), 2.25-2.30 (3H, m, methylene

CH_2), 2.38-2.45 (2H, m, methylene CH_2), 4.12 (2H, q, OCH_2CH_3), 7.43-7.54 (3H, m, Ar-H), 7.59-7.62 (2H, m, Ar-H), 8.87 (1H, s, NH). *m/z* (EI) 337 (M^+, 37 %), 283, 237, 228, 211, 104, 77.



Polyacrylonitrile

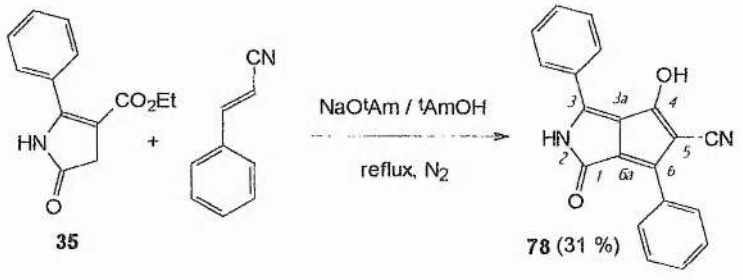
To pre-dried *t*-amyl alcohol (40 ml) was added sodium (1.0 g, 0.0435 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The solution was cooled to 60-65 °C then acrylonitrile (10.0 g) was added slowly. A white precipitate rapidly formed. The mixture was stirred at 30 °C for 3 h and then was added to a mixture of water (100 ml) and concentrated hydrochloric acid (5 ml). The white solid was filtered off, washed with water and dried *in vacuo*. Yield 7.13 g. ν/cm^{-1} 3342 (broad, water O-H), 2200 and 2245 (C≡N).



3,3-Bis-(2-cyanopropyl)-4-ethoxycarbonyl-5-phenyl-4-pyrrolin-2-one 76

Method (a). To pre-dried *t*-amyl alcohol (50 ml) was added sodium (1.20 g, 0.0522 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (4.0 g, 0.0173 mol) and methacrylonitrile (6.0 g, 0.0894 mol) were then added at 25 °C and the mixture was heated to reflux for 3 h then at 25 °C for 16 h. The red-brown solution was then added to an ice-cooled mixture of water (150 ml) and concentrated hydrochloric acid (6 ml). The beige solid precipitate was filtered off then recrystallised from propan-2-ol and dried *in vacuo* at 100 °C. Yield 3.22 g (51 %).

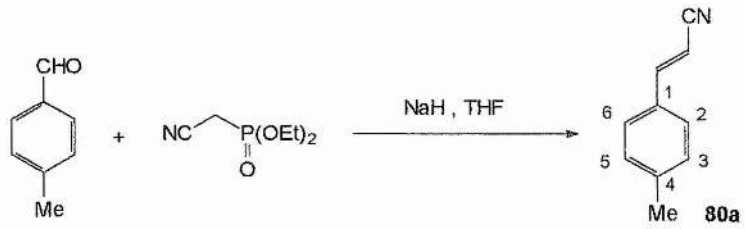
Method (b). To a solution of the lactam ester **35** (1.0 g, 0.0043 mol) in tetrahydrofuran (70 ml) under nitrogen was added sodium hydride (60 % w/w mineral oil dispersion, 0.36 g, 0.0090 mol). The mixture was heated briefly to reflux then cooled to 25 °C upon which a white precipitate formed. Methacrylonitrile (1.44 g, 0.0215 mol) was then added, the mixture was then briefly reheated to reflux then stirred at 25 °C for 16 h during which time the precipitate redissolved. The solution was added to ice, extracted with tetrahydrofuran / diethyl ether, dried (Na_2SO_4), concentrated and the colourless solid was dried *in vacuo*. Flash chromatography on silica gel H eluted with 5% methanol / dichloromethane then methanol yielded a colourless solid. Yield 1.02 g (65 %), m.p. 211-213 °C. (Found: C, 69.0; H, 6.5; N, 11.4. $C_{21}H_{23}N_3O_3$ requires C, 69.0; H, 6.3; N 11.5 %). ν/cm^{-1} 3222 (N-H), 2238 (C≡N), 1739 (C=O), 1656 (C=O). The ^{1}H NMR spectrum was identical at both -50 °C and at +40 °C, indicating that the conformation of the alkyl side chains did not account for the complex pattern observed at δ_H 2.10-2.74. The spectrum may not be first order.δ_H 1.10 (3H, t, J 7.0, OCH_2CH_3), 1.28-1.51 (6H, m, 2 x CH_3), 1.85 (1H, dt, J 3.0 and 13.1, CH_2CH), 2.10-2.74 (5H, m, CH_2CH and CH_2CH), 4.15 (2H, q, OCH_2CH_3), 7.42-7.46 (2H, m, *m-/p-* Ar-H), 7.66-7.70 (2H, m, *o-* Ar-H), 8.47 (1H, s, NH). See Appendix 4 (page 163) for details of X-ray structure analysis.



5-Cyano-4-hydroxy-3,6-diphenyl-2*H*-cyclopenta[*c*]pyrrol-1-one 78

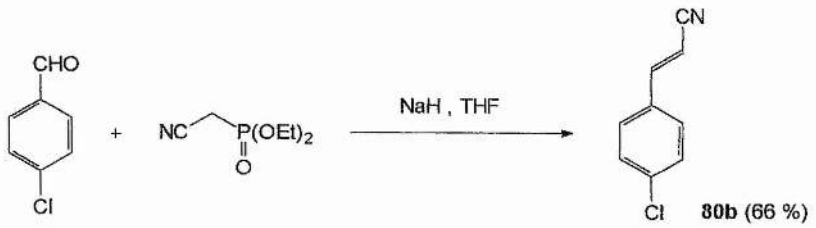
To pre-dried *t*-amyl alcohol (200 ml) was added sodium (5.66 g, 0.2462 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (17.90 g, 0.0774 mol) was added, then cinnamonitrile (10.02 g, 0.0776 mol) was added portionwise over 30 min during which time a purple-red solution formed. Stirring was continued for 2 h at reflux, then for 15 h at 25 °C and the solution was added to an ice-cooled mixture of methanol (150 ml) and concentrated hydrochloric acid (25 ml). The dark red solid

was filtered off, washed with methanol and water then dried *in vacuo*. Yield 7.39 g (31 %), m.p. 273-275 °C. (Found: C, 77.1; H, 3.8; N, 8.9. $C_{20}H_{12}N_2O_2$ requires C, 76.9; H, 3.9; N, 9.0 %). λ_{max} /nm (DMSO) 457nm (ε 3946), 509 (2270). ν/cm^{-1} 3114 (strong, N-H or O-H), 2205 (C≡N), 1667 (C=O), 1600. δ_H (DMSO-d_6) 7.45-7.57 (6H, m, *m-/p-* Ar-H), 8.23 (2H, dd, J 1.5 and 8.0, *o-* Ar-H), 8.33-8.36 (2H, m, *o-* Ar-H), 11.01 (1H, s, NH, reduced on D_2O exchange). *m/z* 312.1003 ($M^{+\cdot}$, 100%, $C_{20}H_{12}N_2O_2$ requires 312.0899).



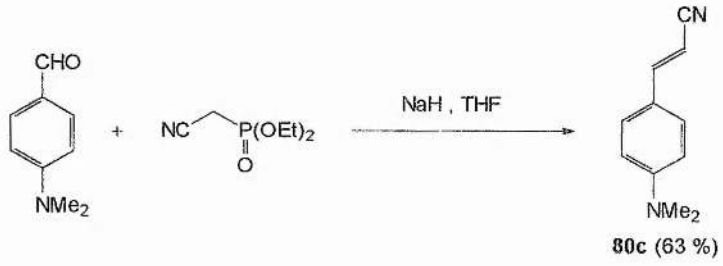
4-Methylcinnamonitrile 80a

To a suspension of sodium hydride (60 % w/w mineral oil dispersion, 1.70 g, 0.0425 mol) in tetrahydrofuran (50ml) under nitrogen, diethyl cyanomethylphosphonate (7.45 g, 0.0421 mol) was added dropwise over 10 min. The colourless solution was cooled to 4 °C, then 4-tolualdehyde (5.04 g, 0.0419 mol) was added dropwise as a solution in tetrahydrofuran (20 ml) over 15 min. The mixture was stirred at 25 °C overnight with exclusion of moisture, then added to ice-water, extracted with diethyl ether, dried (Na_2SO_4), concentrated and the beige solid was washed with cold hexane and dried *in vacuo*. Yield 5.53 g (92 %), m.p. 71-73 °C (lit.[120] 70-71 °C). δ_H (200MHz) E isomer 2.89 (3H, s, Ar-CH_3), 5.82 (1H, d, J 16.7, C*H*CN), 7.21 (2H, d, J 8.1, Ar H-3 and -5), 7.37 (1H, d, C*H*CHCN), 7.37 (2H, d, Ar H-2 and -6); *Z* isomer assignment not complete (resonances obscured by E-isomer). *E* / *Z* ratio 10 : 1. ν/cm^{-1} 2215 (C≡N), 1618 (C=C).



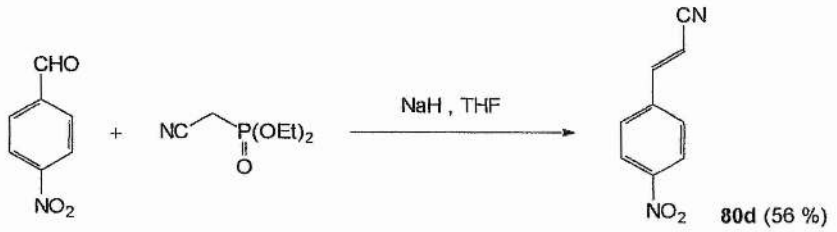
4-Chlorocinnamonitrile 80b

The procedure was completed as described below for 4-nitrocinnamonitrile and gave a beige solid product: recrystallised from propan-2-ol. Yield 2.29 g (66 %), m.p. 85-86 °C (lit.[120] 84-87 °C). δ_H *E* isomer 5.86 (1H, d, J_{trans} 16.4, C*H*CN), 7.36 (1H, d, C*H*CHCN), 7.37-7.46 (4H, m, Ar-H); *Z* isomer 5.48 (1H, d, J_{cis} 11.8, C*H*CN), 7.09 (1H, d, C*H*CHCN), 7.45 (2H, d, Ar H-3 and -5), 7.75 (2H, d, J_{ortho} 8.0, Ar H-2 and -6). *E* / *Z* ratio = 5 : 1. ν/cm^{-1} 2217 (C≡N), 1625 (C=C), 1591.



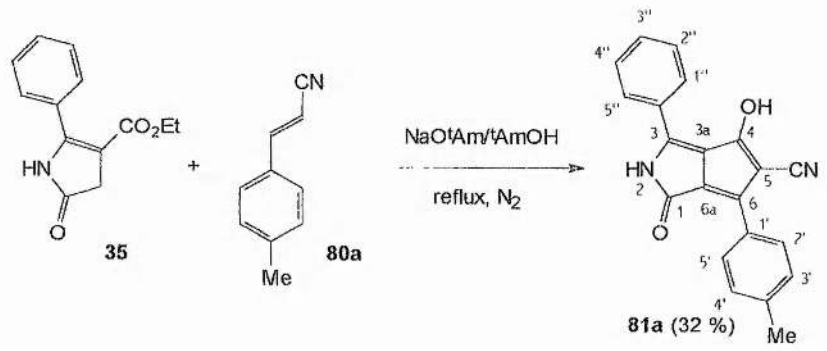
4-Dimethylaminocinnamonitrile 80c

The procedure was completed as described below for 4-nitrocinnamonitrile and gave a beige solid product (2.18 g, 63 %), m.p. 158-160 °C (lit.[121] 163.5 °C) δ_H *E* isomer 3.03 [6H, s, N(C*H*$_3$)$_3$], 5.58 (1H, d, J_{trans} 17.6, C*H*CN), 6.66 (2H, d, J_{ortho} 8.8, Ar H-3 and -5), 7.28 (1H, d, C*H*CHCN), 7.32 (2H, d, Ar H-2 and -6); *Z* isomer 3.04 [6H, s, N(CH$_3$)$_3$], 5.09 (1H, d, J_{cis} 12.1, CHCN), 6.68 (2H, d, Ar H-3 and -5), 6.94 (1H, d, C*H*CHCN), 7.75 (2H, d, J_{ortho} 9.1, Ar H-2 and -6). *E* / *Z* ratio = 3.6 : 1. ν/cm^{-1} 2181 (C≡N), 1600 (C=C).



4-Nitrocinnamonitrile 80d

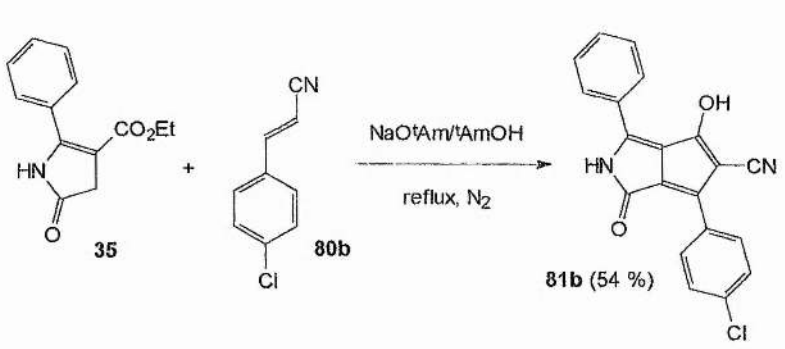
To a suspension of sodium hydride (60 % w/w mineral oil dispersion, 0.58 g, 0.0145 mol) in tetrahydrofuran (50ml) under nitrogen was added diethyl cyano-methylphosphonate (2.34 g, 0.0132 mol) dropwise over 10 min. The colourless solution was cooled to 4 °C, then 4-nitrobenzaldehyde (2.01 g, 0.0133 mol) was added dropwise as a solution in tetrahydrofuran (20 ml) over 15 min. The mixture was stirred at 25 °C overnight with exclusion of moisture, then added to ice-water, extracted with diethyl ether, and the extract dried (Na_2SO_4), concentrated and the beige solid was washed with cold hexane and dried *in vacuo*. Yield 1.28 g (56 %), m.p. 200-202 °C (lit.[120] 200 °C). δ_H (200MHz) *E* isomer: 6.06 (1H, d, J_{trans} 17.5, CHCN), 7.64 (2H, m, J_{ortho} 8.8, Ar H-2 and -6), 7.48 (1H, d, C*H*CHCN), 8.29 (2H, m, Ar H-3 and -5). *Z* isomer: assignment not complete (resonances obscured by E-isomer). *E* / *Z* ratio = 2.5 : 1. ν/cm^{-1} 2218 (C≡N), 1630 (C=C), 1602, 1526 (C-NO_2 asymmetric), 1333 (C-NO_2 symmetric).



5-Cyano-4-hydroxy-3-(4-tolyl)-2*H*-cyclopenta[*c*]pyrrol-1-one 81a

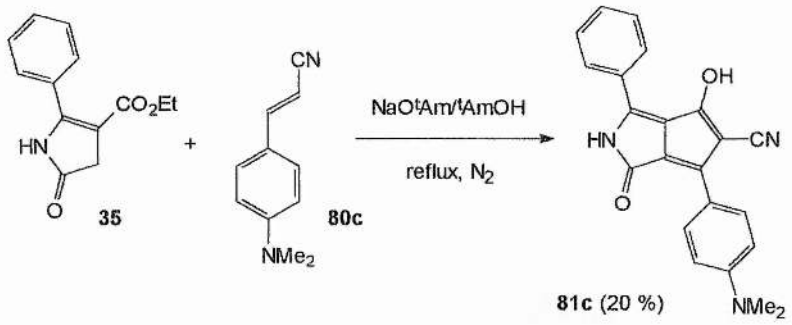
To pre-dried *t*-amyl alcohol (150 ml) was added sodium (1.72 g, 0.0748 mol) with stirring under nitrogen and the mixture was heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (4.85 g, 0.0210 mol) was added, then nitrile **80a** (3.0 g, 0.0210 mol) was added portionwise over 30 min during which time a

dark red solution formed. Stirring was continued for 2 h at reflux, then for 15 h at 25 °C and the solution was added to an ice-cooled mixture of water (70 ml), methanol (10 ml) and concentrated hydrochloric acid (7.5 ml). The dark red solid was filtered off, washed with water then methanol and dried *in vacuo*. Yield 2.22 g (32 %). (Found: C, 77.5; H, 4.4; N, 8.6. $C_{21}H_{14}N_2O_2$ requires C, 77.3; H, 4.3; N, 8.6 %). ν/cm^{-1} 3114 (weak, N-H or O-H), 2209 (C≡N), 1668 (C=O). δ_H (DMSO-d_6) 2.37 (3H, s, CH_3), 7.31 (2H, d, J = 8.2, H-3' and -5'), 7.55-7.57 (3H, m, H-3", -4" and -5"), 8.15 (2H, dd, J 1.9 and 8.0, H-2' and -6'), 8.29-8.32 (2H, m, H-2" and -6"), 11.04 (1H, s, NH).



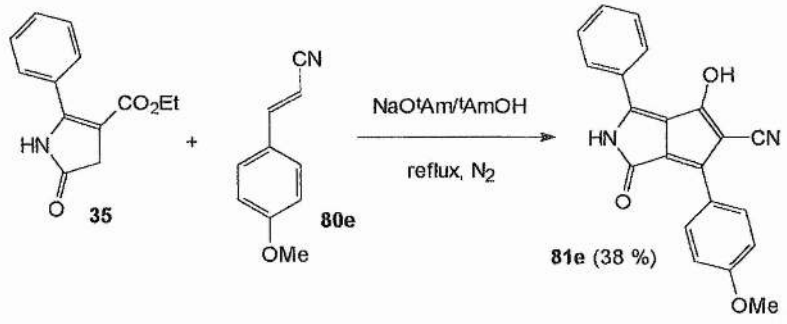
5-Cyano-4-hydroxy-3-(4'-chlorophenyl)-6-phenyl-2*H*-cyclopenta[*c*]pyrrol-1-one 81b

To pre-dried *t*-amyl alcohol (40 ml) was added sodium (0.81 g, 0.0352 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (2.33 g, 0.0101 mol) then nitrile **81b** (1.65 g, 0.0101 mol) were added at 75-80 °C. Heating to reflux was continued for 2 h, during which time a purple-red solution formed. The solution was added to an ice-cooled mixture of methanol (100 ml) and concentrated hydrochloric acid (3.6 ml), then the purple-red solid was filtered off, washed with methanol and water then dried *in vacuo*. Yield 1.90 g (54%), m.p. 290-292 °C. (Found: C, 69.0; H, 3.3; N, 7.8. $C_{20}H_{11}ClN_2O_2$ requires C, 69.3; H, 3.2; N, 8.1 %).ν/cm^{-1} 3370 (broad, N-H or O-H), 2208 (C≡N), 1600 (C=O). δ_H (DMSO-d_6) 7.51-7.58 (5H, m, Ar-H), 8.25-8.28 (2H, m, Ar-H), 8.33-8.36 (2H, m, Ar-H), 11.04 (1H, s, NH). λ_{max} /nm (DMSO) 461 (ε 14872), 605 (7907) and addition of triethylamine (3 drops) made no difference to the electronic spectrum. *m* / *z* 346 ($M^{+\cdot}$).



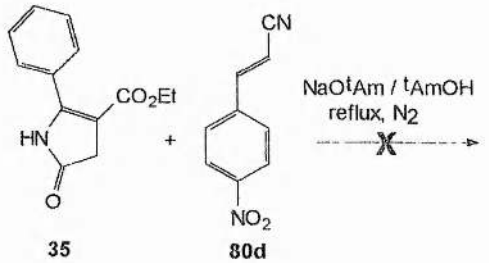
4-Hydroxy-3-(4'-dimethylaminophenyl)-6-phenyl-2*H*-cyclopenta[*c*]pyrrol-1-one-5-carbonitrile 81c

To pre-dried *t*-amyl alcohol (40 ml) was added sodium (0.84 g, 0.0352 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (2.69 g, 0.0116 mol) was added at 85-90 °C, then nitrile **80c** (2.00 g, 0.0116 mol) was added portionwise over 40 min. at reflux during which time a purple solution formed. Stirring was continued for 1.5 h then the solution was added to an ice-cooled mixture of methanol (90 ml) and concentrated hydrochloric acid (4 ml); the purple-red solid was filtered off, washed with methanol and water then dried *in vacuo*. Yield 0.81 g (20 %). ν/cm^{-1} 3110 (weak, N-H or O-H), 2202 (C≡N), 1657 (C=O), 1600. (Found: C, 72.5; H, 4.6; N, 11.5. $C_{22}H_{17}N_3O_2$ requires C, 74.4; H, 4.8; N, 11.8 %). δ_H 3.05 (6H, s, $N(CH_3)_2$), 6.83-6.86 (2H, m, Ar-H), 7.43-7.52 (3H, m, Ar-H), 8.24-8.33 (4H, m, Ar-H), 11.16 (1H, s, NH). *m/z* 355 ($M^{+\cdot}$, 13 %), 324, 169, 77 with trace amount of material at 379. λ_{max} /nm (DMSO) 482 (ε 6472), 583 (2829) and addition of triethylamine (3 drops) made no difference to the electronic spectrum.



4-Hydroxy-3-(4'-methoxyphenyl)-6-phenyl-2*H*-cyclopenta[*c*]pyrrol-1-one-5-carbonitrile 81e

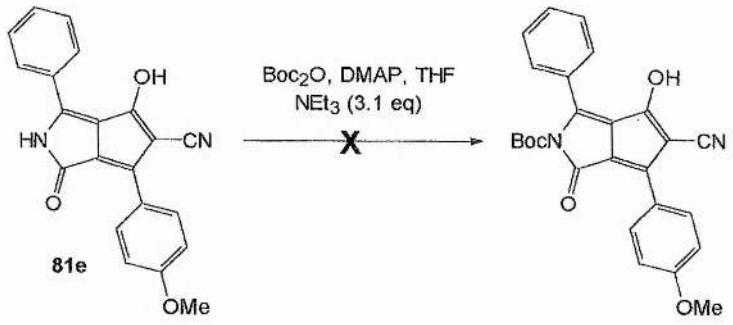
To pre-dried *t*-amyl alcohol (70 ml) was added sodium (0.86 g, 0.0374 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (2.86 g, 0.0124 mol) then nitrile **80e** (2.01 g, 0.0126 mol) were then added and the mixture was heated to reflux for 3 h, during which time a purple-red solution formed. The solution was added to an ice-cooled mixture of methanol (40 ml) and concentrated hydrochloric acid (4 ml), the purple-red solid filtered off, washed with methanol and water then dried *in vacuo*. Yield 1.63 g (38 %), m.p. 286-287 °C. (Found: C, 73.5; H, 3.9; N, 8.1. $C_{21}H_{14}N_2O_3$ requires C, 73.7; H, 4.1; N, 8.2 %).δ_H (DMSO-d_6) 3.84 (3H, s, OCH_3), 7.09 (2H, d, J 9.0, *o*- Ar-H), 7.55-7.57 (3H, m, Ar-H), 8.27 -8.31 (4H, m, Ar-H), 11.13 (1H, s, NH). λ_{max}/nm (DMSO) 460 (ε 13309), 592 (5927). λ_{max}/nm (DMSO + 1 drop conc. HCl) 492 (12876). ν/cm^{-1} 3110 (N-H or O-H), 2208 (C≡N), 1673 (C=O), 1611. *m z* 342.1009 ($M^{+\cdot}$, 100%, $C_{21}H_{14}N_2O_3$ requires 342.1004).



Attempted reaction of the lactam ester 35 with nitrile 80d

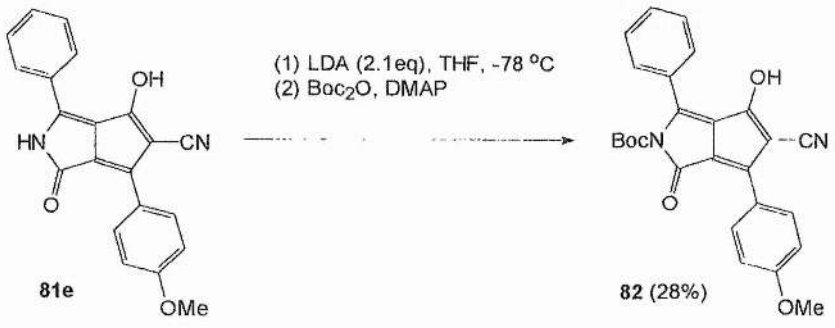
To pre-dried *t*-amyl alcohol (20 ml) was added sodium (0.40 g, 0.0174 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (1.29 g, 0.0056 mol) and nitrile **80d** (1.0 g,

0.0057 mol) were then added and the mixture was heated to reflux for 1.5 h. Stirring was continued at 25 °C for 16 h and then the mixture was added to methanol / water and acidified with dilute hydrochloric acid. The brown precipitate was filtered off and dried *in vacuo*. This intractable material was not soluble in DMSO for NMR analysis and was not intensely coloured.



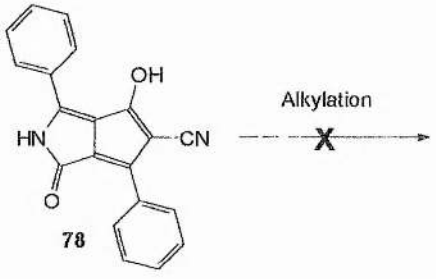
Attempted reaction of 81e with Boc_2O

A mixture of compound **81e** (0.3 g, 0.9 mmol), tetrahydrofuran (20 ml), DMAP (0.08 g, 0.7 mmol) and Boc_2O (0.25 g, 1.1 mmol) was stirred at 25 °C with the exclusion of moisture. Triethylamine (0.11 g, 1.1 mmol) was added after 10 h, then further Boc_2O was added after 10 h (0.26g, 1.2 mmol), and after 24 h (0.34 g, 1.6 mmol). Further portions of triethylamine were similarly added after 24 h (0.07 g, 0.7 mmol), and after 48 h (0.10 g, 1 mmol). The mixture was analysed by tlc during several days, but only trace amounts of fluorescent spots were evident, with most of the mixture remaining as baseline. After several days the mixture was concentrated, and ^1H NMR indicated only unreacted starting material.



2-*t*-Butoxycarbonyl-5-cyano-4-hydroxy-3-(4'-methoxyphenyl)-6-phenyl-cyclopenta[*c*]pyrrol-1-one 82

A solution of *n*-butyllithium in hexanes (1M, 1.0 ml, 0.0025 mol) was added with stirring, under nitrogen, to a flask charged with tetrahydrofuran (25ml) and diisopropylamine (0.42 g, 0.0042 mol) and stirring continued for 1.5 h. The solution was cooled to -78 °C then added dropwise to a mixture of derivative **81e** and tetrahydrofuran (20 ml) at -78 °C under nitrogen. This purple coloured solution was stirred at -78 °C for 30 min. then Boc_2O (0.41 g, 0.0018 mol) was added in tetrahydrofuran (1.5 ml). The mixture was left to warm to 25 °C during 1 h then heated to reflux (65 °C) for 45 min. Further Boc_2O (0.71 g, 0.0033 mol) then DMAP (0.09 g, 0.0007 mol) were added and stirring continued for 20 h. Saturated aqueous ammonium chloride solution (6ml) was then added, the mixture acidified to pH 6-7 with 10 % hydrochloric acid, extracted with diethyl ether, dried over sodium sulfate then concentrated to dryness. Flash chromatography on silica gel H eluted with petrol / ethyl acetate (1:1), then methanol yielded a purple solid, which was dried *in vacuo*. Yield 0.16 g (28%). The product decomposed without melting. δ_H (200MHz, DMSO-d_6), 1.25 [9H, s, $O(CH_3)_3$], 3.83 (3H, s, OCH_3), 7.01-7.06 (2H, m, Ar-H), 7.37-7.49 (3H, m, Ar-H), 7.62-7.68 (2H, m, Ar-H), 8.33-8.38 (2H, m, Ar-H). ν/cm^{-1} 2190 (C≡N), 1716 (C=O), 1644, 1606.



78

Attempted reaction of 78 with methyl tosylate

A mixture of compound **78** (0.50 g, 0.0016 mol), potassium carbonate (0.45 g, 0.0033 mol), methyl tosylate (0.60 g, 0.0032 mol) and nitrobenzene (35 ml) was heated to reflux (200°C) under nitrogen. The mixture was then concentrated (Kugelrohr) to yield a dark red-brown intractable solid.

Attempted reaction of 78 with triethyloxonium tetrafluoroborate

A mixture of compound **78** (0.89 g, 28 mmol), tetrahydrofuran (20 ml) and triethyloxonium tetrafluoroborate (0.58 g, 31 mmol) was stirred at 25 °C under nitrogen for 72 h. No colour change from that of the starting reagent **78** was

observed. The mixture was added to ice-water and the red precipitate was then filtered off, washed with water then methanol then dried *in vacuo*. Yield 0.56 g). ^{1}H NMR showed only unreacted starting material **78**.

Attempted reaction of 78 with trimethyloxonium tetrafluoroborate

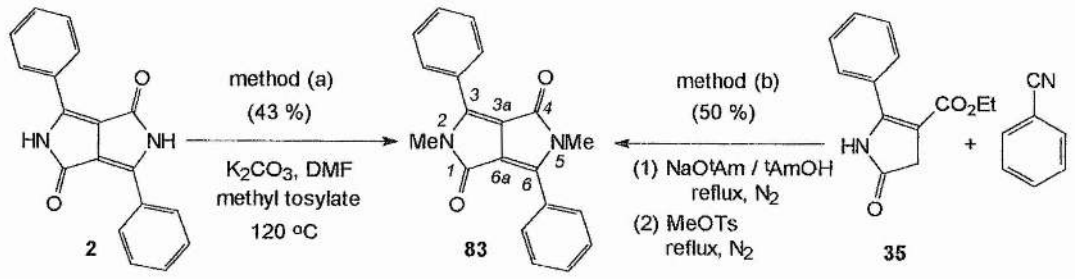
To a stirred mixture of sodium hydride (0.0975 g, 16 mmol) and dichloromethane (20 ml) was added compound **78** (0.5075 g, 24 mmol) and trimethyloxonium tetrafluoroborate (0.33 g, 22 mmol). The mixture was stirred at 25 °C with the exclusion of moisture and then was added to ice-water. The red precipitate was filtered off, washed with water then dried *in vacuo*. Yield 0.37 g. ^{1}H NMR showed only unreacted starting material **78**.

Attempted reaction of 78 with triethyloxonium tetrafluoroborate

To a stirred mixture of sodium hydride (0.0909 g, 22 mmol) and dichloromethane (20 ml) was added compound **78** (0.5016 g, 16 mmol) and triethyloxonium tetrafluoroborate (0.44 g, 23 mmol). The mixture was stirred at 25 °C with the exclusion of moisture and then was added to ice-water. The red precipitate was filtered off, washed with water then dried *in vacuo*. Yield 0.46 g. ^{1}H NMR showed only unreacted starting material **78**.

Attempted reaction of 78 with triethyloxonium tetrafluoroborate

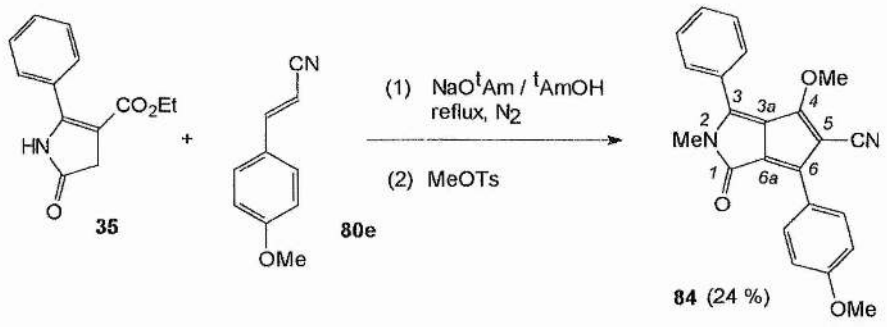
To a stirred mixture of compound **78** (0.21 g, 0.7 mmol) and tetrahydrofuran (25 ml) under nitrogen was added lithium hexamethyldisilazide (2.0 ml, 2 mmol). A dark purple coloured suspension in a purple solution was formed. The mixture was heated to reflux for 5 min then stirred at 25 °C for 1 h. Triethyloxonium tetrafluoroborate (0.40 g, 21 mmol) was then added and the mixture was stirred at 25 °C for 2 h. The colour changed to give a dark orange solution. The mixture was added to aqueous ammonium chloride (50 ml), extracted with tetrahydrofuran-ethyl acetate, then dried (Na_2SO_4), concentrated and dried *in vacuo*. Yield 0.34 g. ^{1}H NMR of the crude product provided evidence to show loss of the NH resonance (δ_H11.01) and the presence of an ethyl ester indicating that some alkylation had occurred. Recrystallisation from propan-2-ol and attempts at flash chromatography on silica gel H eluted with petrol-ethyl acetate did not provide sufficiently pure material.



2,5-Dimethyl-3,6-diphenyl-DPP 83

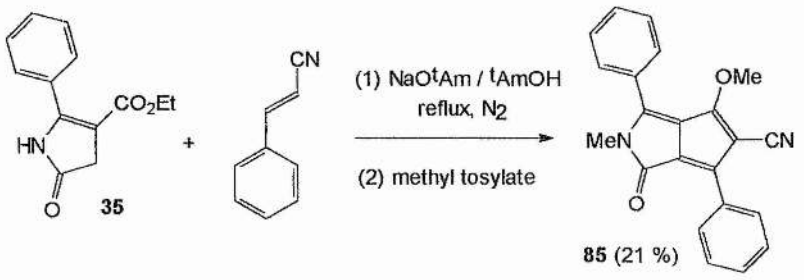
Method (a) A mixture of 3,6-diphenyl-DPP **2** (0.50 g, 0.0017 mol), potassium carbonate (3.0 g, 0.0217 mol) and *N,N*-dimethylformamide (35 ml) was stirred at 120 °C for 3.5 h with exclusion of moisture. Methyl 4-toluenesulfonate (3.70 g, 0.0199 mol) was then added as a solution in DMF (5 ml) and stirring continued with heating for 3.5 h. The mixture was cooled then added to water (100 ml) and the precipitate was filtered off, washed with water, and dried *in vacuo*. Recrystallisation from toluene yielded red-orange crystals (0.23 g, 43 %), m.p. 228-230 °C (lit.[56] 233-234 °C).

Method (b) To pre-dried *t*-amyl alcohol (20 ml) was added sodium (0.33 g, 0.0144 mol) with stirring under nitrogen and the mixture was heated to reflux (105- 110 °C) until all the sodium dissolved. The lactam ester **35** (1.02 g, 0.0044 mol) and benzonitrile (1.0 g, 0.0097 mol) were then added and heating to reflux maintained for 5 h during which time a bright red precipitate gradually formed. The mixture was cooled to 80-90 °C then methyl 4-toluenesulfonate (9.20 g, 0.0494 mol) was added portionwise. Heating was continued for 45 min during which time the mixture turned fluorescent yellow. The mixture was then added to water (50ml), extracted with ethyl acetate, washed with water, concentrated and the red-orange solid product was filtered off, washed with methanol and dried *in vacuo* at 60 °C. Yield 0.69 g (50 %). δ_H (200 MHz,) 3.33 (6H, s, NCH_3), 7.50-7.54 (6H, m, *m-/p-* Ar-H), 7.84-7.89 (4H, m, *o-* Ar-H). δ_C 29.85 (NCH_3), 109.62 (C-3, -6), 128.35 (*ipso* Ar-C), 129.25, 129.54, 131.69 (Ar-C), 149.00 (C-3a, -6a), 163.03 (C-1, -4).



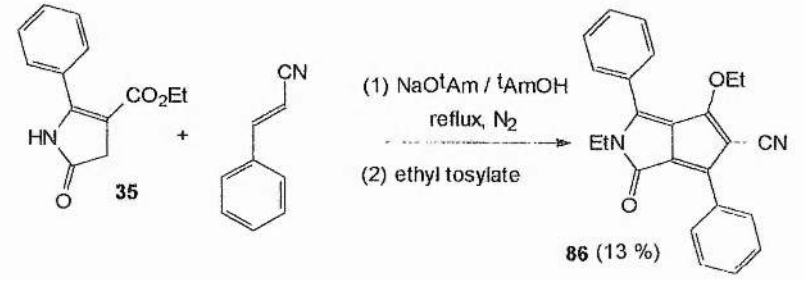
5-Cyano-*N*-methyl-4-methoxy-6-(4-methoxyphenyl)-3-phenyl-cyclopenta[*c*]pyrrol-1-one 84

To pre-dried *t*-amyl alcohol (25 ml) was added sodium (0.79 g, 0.0344 mol) with stirring under nitrogen and the mixture was heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (2.56 g, 0.0111 mol) then 4-methoxycinnamonitrile **80e** (2.09 g, 0.0131 mol) were added and heating to reflux continued for 4 h during which time a dark purple coloured solution developed. The mixture was cooled to 40 °C, then methyl tosylate (20.32 g, 0.1091 mol) was added portionwise during 10 min. Heating to reflux was continued for 45 min, during which time the colour changed to a bright red-orange. The mixture was cooled, added to water (50 ml), extracted with ethyl acetate, washed with water then concentrated. The solid product was filtered off, washed with methanol then petrol and dried *in vacuo*. Recrystallisation from 1,4-dioxan yielded red-orange fibrous crystals (0.97 g, 24 %); m.p. 253-255 °C. (Found: C, 74.7; H, 4.8; N, 7.4. $C_{23}H_{18}N_2O_3$ requires C, 74.6; H, 4.9; N, 7.7 %).δ_H 3.19 (3H, s, NCH_3), 3.88 (3H, s, $ArOCH_3$), 4.20 (3H, s, 4-OCH_3), 7.00 (2H, d, J 8.8, Ar-H), 7.54-7.62 (5H, m, Ar-H), 8.33 (2H, d, J 8.8, Ar-H). *m* / *z* 370.1324 ($M^{+\cdot}$, 100%, $C_{23}H_{18}N_2O_3$ requires 370.1317), 355 (39), 77 (8), ν/cm^{-1} 2200 (C≡N), 1701 (C=O), 1607. See Appendix 5 (page 169) for details of X-ray structure analysis.



N-methyl-4-methoxy-3,6-diphenyl-cyclopenta[*c*]pyrrol-1-one-5-carbonitrile 85

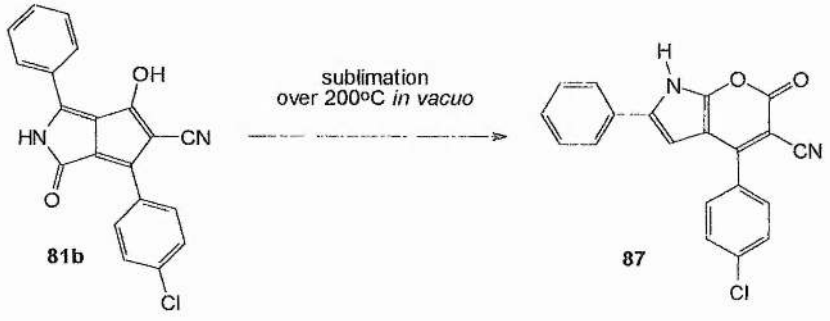
To pre-dried *t*-amyl alcohol (50 ml) was added sodium (1.22 g, 0.0531 mol) with stirring under nitrogen and the mixture was heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (4.0 g, 0.0173 mol) then cinnamonitrile (4.46 g, 0.0345 mol) were added and heating to reflux continued for 4.5 h during which time a purple-red coloured solution developed. The mixture was cooled to 25 °C, then methyl tosylate (25.22 g, 0.1354 mol) was added. Heating to reflux was continued for 1 h. The mixture was cooled, added to water (100 ml), extracted with ethyl acetate, dried (Na_2SO_4) then concentrated. The residue obtained was dissolved in sodium ethoxide / ethanol solution overnight and reprecipitated by addition to water and acidification with concentrated hydrochloric acid dropwise. Recrystallisation from propan-2-ol / tetrahydrofuran yielded a red-orange solid (1.22 g, 21 %); m.p. 210-212 °C. (Found: C, 77.3; H, 4.7; N, 8.2. $C_{22}H_{16}N_2O_2$ requires C, 77.6; H, 4.7, N, 8.2 %). δ_H 3.18 (3H, s, NCH_3), 4.21 (3H, s, OCH_3), 7.43-7.66 (8H, m, Ar-H), 8.22 (2H, d, J 6.6, Ar-H). ν/cm^{-1} 2197 (C≡N), 1703 (C=O), 1677. *m/z* 340 ($M^{+\cdot}$, 100%), 325 (76), 77 (15) with trace amount of material at 354.



N-Ethyl-4-ethoxy-3,6-diphenyl-cyclopenta[*c*]pyrrol-1-one-5-carbonitrile 86

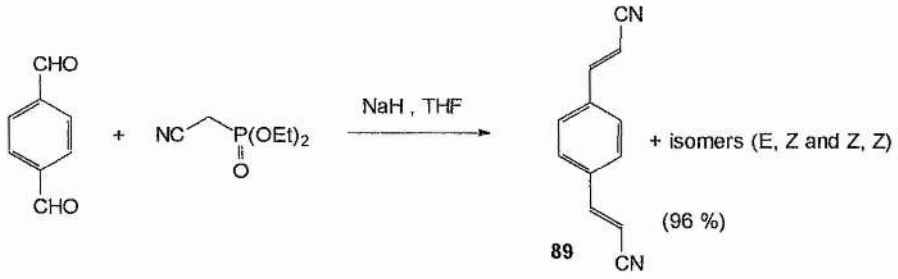
To pre-dried *t*-amyl alcohol (80 ml) was added sodium (4.50 g, 0.1957 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the

sodium dissolved. The lactam ester **35** (15.0 g, 0.0649 mol) then cinnamonitrile (8.40 g, 0.0650 mol) were added and heating to reflux was continued for 1.5 h during which time a purple-red coloured solution developed. Ethyl tosylate was then added during 30 min as a solution in DMF (20 ml) and heating continued for a further 1.5 h, during which the solution changed to an orange colour and a white precipitate was formed. The mixture was cooled, added to water (250 ml), then extracted with ethyl acetate, acidified with 10 % hydrochloric acid and concentrated. The orange residue was dissolved overnight in sodium ethoxide / ethanol solution and reprecipitated by addition to 10% hydrochloric acid. The red-orange product was filtered, washed with water and dried *in vacuo*. Yield 3.07 g (13 %), m.p. 200-202 °C. (Found: C, 78.0; H, 5.2; N, 7.8 %. $C_{24}H_{20}N_2O_2$ requires C, 78.2, H, 5.5; N, 7.6 %). ν/cm^{-1} 2195 (C≡N), 1694 (C=O), 1655. δ_H (200 MHz) 1.19 (3H, t, J 7.1, CH_2CH_3), 1.29 (3H, t, CH_2CH_3), 3.68 (2H, q, NCH_2CH_3), 4.55 (2H, q, OCH_2CH_3), 7.42-7.67 (8H, m, Ar-H), 8.22 (2H, dd, J 2.2 and 8.2, *o*- Ar-H). *m z* 368 ($M^{+\cdot}$, 50 %), 340 (35), 325 (7).



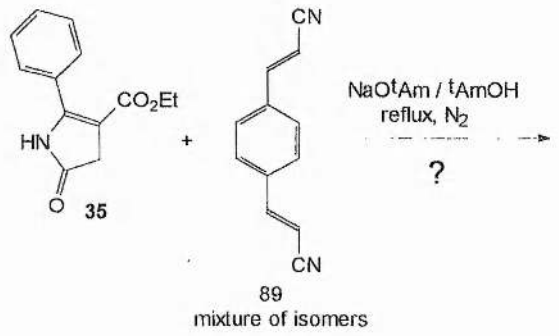
Derivative 87 from sublimation of compound 81b

A sample of compound **81b** (0.1 g) was heated under vacuum (approx. 1.7 x 10^{-2} Torr) at over 200 °C for several hours in a cold finger apparatus. λ_{max} /nm (DMSO) 424 (ε 9132). δ_H 6.71 (1H, s, CH), 7.27-7.31 (2H, m, Ar-H), 7.38-7.43 (2H, m, Ar-H), 7.71-7.78 (5H, m, Ar-H), 8.48 (1H, br.s., NH). See Appendix 6 (page 174) for details of X-ray structure analysis.



3,3'-(*p*-Phenylenedi)-acrylonitrile 89

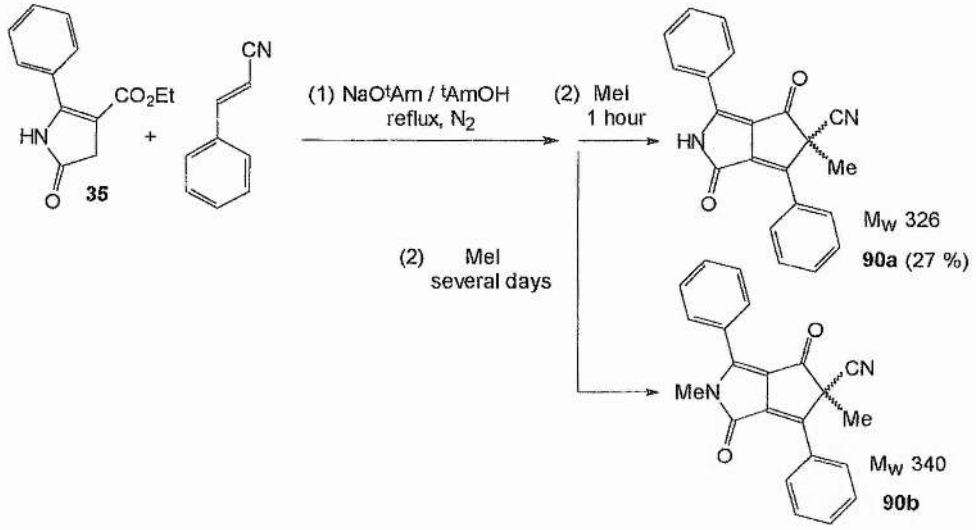
To a suspension of sodium hydride (60 % w/w mineral oil dispersion, 0.66 g, 0.0165 mol) in tetrahydrofuran (30 ml) under nitrogen was added diethyl cyanomethylphosphonate (2.66 g, 0.0150 mol). The colourless solution was cooled to 4 °C then 1,4-terephthaldicarboxaldehyde (1.0 g, 0.0074 mol) was added dropwise as a solution in tetrahydrofuran (30 ml). A dark grey colouration developed. Stirring was continued at 25 °C for 72 h then the mixture was added to ice, extracted with a tetrahydrofuran/diethyl ether mixture, concentrated and washed with hexane. Recrystallisation from aqueous ethanol yielded a beige solid (1.29 g, 96 %), m.p. partial melting at 180-185 °C with full melting at 228-230 °C. ν/cm^{-1} 2216 (C≡N), 1618 (C=C). δ_H (partial assignment) *E,E* isomer 5.56 (2H, d, J 12.2, CHC*H*CN), 7.14 (2H, d, C*H*CHCN), 7.86 (4H, d, J 8.4, Ar-H); *Z,Z* isomer 5.96 (2H, d, J 16.4, CHC*H*CN), 7.41 (2H, d, C*H*CHCN), 7.51 (4H, s, Ar-H). *E,E* / *Z,Z* ratio = 4:1.



Attempted reaction of the lactam ester 35 with nitrile 89

To pre-dried *t*-amyl alcohol (30 ml) was added sodium (0.38 g, 0.0165 mol) with stirring under nitrogen and the mixture heated at reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (1.28 g, 0.0055 mol) then nitrile **89** (0.5 g, 0.0028 mol) were added and the mixture was heated to reflux for 3 h. The mixture was then added to an ice-cooled mixture of water (100 ml), methanol (10 ml) and

concentrated hydrochloric acid (2 ml). The purple precipitate was filtered off, washed with methanol then water and dried *in vacuo*. Yield 0.84 g. δ_H (DMSO-d_6) (partial assignment) 7.18-7.58 (m, Ar-H), 8.18-8.47 (m, Ar-H), 11.08 (s, NH) with small resonances at 10.67, 10.90, 11.16 (s, NH?) and further trace impurities in region 1.00-4.15 consistent with an ethyl ester.



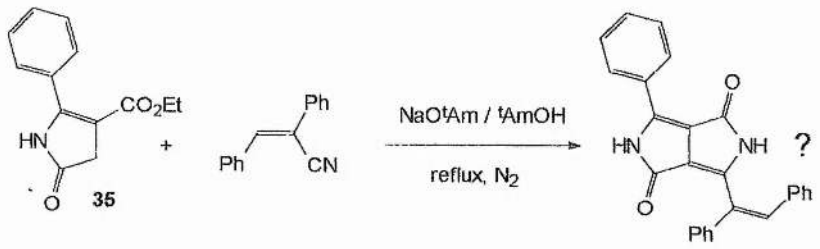
Reaction of the lactam ester 35 with cinnamonitrile to yield 90a

To pre-dried *t*-amyl alcohol (20 ml) was added sodium (0.60 g, 0.0261 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (2.0 g, 0.0086 mol) then cinnamonitrile (1.19 g, 0.0092 mol) were added and heating to reflux was continued for 4.5 h during which time a purple-red coloured solution developed. The mixture was then cooled to 55 °C and methyl iodide (5.5 g, 0.0387 mol) was added. Heating was continued at 40 °C for 1 h, then the mixture was added to water, acidified with 10 % hydrochloric acid, extracted with ethyl acetate then dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel H eluted with petrol / ethyl acetate (2:1) yielded a fluorescent orange solid which was recrystallised from a propan-2-ol/ tetrahydrofuran mixture then dried *in vacuo*. Yield 0.76 g (27 %), m.p. 299-301 °C. (Found: C, 77.3; H, 4.4; N, 8.4 %. $C_{21}H_{14}N_2O_2$ requires C, 77.3, H, 4.3; N, 8.6 %). ν/cm^{-1} 3167 (NH), 2365 (C≡N), 1677 (C=O), 1607. δ_H 1.90 (3H, s, CCH_3), 7.57-7.65 (6H, m, *m-/p-* Ar-H), 8.41-8.51 (4H, m, *o-* Ar-H), 12.22 (1H, s, NH) with trace

impurity at 3.32 (<<1H, s, NCH_3). m/z 326 ($M^{+\cdot}$, 100 %) with trace amount of product at 340.

Reaction of the lactam ester 35 with cinnamonitrile to yield 90b

To pre-dried *t*-amyl alcohol (80 ml) was added sodium (2.97 g, 0.1292 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (10.0 g, 0.0432 mol) then cinnamonitrile (5.60 g, 0.0434 mol) were added and heating to reflux was continued for 3.5 h, then at 25 °C for 2 h, during which time a purple-red coloured solution developed. Methyl iodide (25.15 g, 0.1772 mol) was then added and the mixture was stirred at 25 °C for 144 h and was then added to water (200 ml), extracted with ethyl acetate and concentrated. Flash chromatography on silica gel H eluted with petrol / ethyl acetate (1:1) afforded a fluorescent orange solid which was dried *in vacuo*. Yield 5.12 g (35 %). This was recrystallised from propan-2-ol / tetrahydrofuran. m.p. 296-298 °C. δ_H 1.87 (3H, s, CCH_3), 3.32 (3H, s, NCH_3), 7.61-7.64 (6H, m, *m-/p-* Ar-H), 7.83-7.87 (2H, m, *o-* Ar-H adjacent to N-CH_3), 8.50-8.53 (2H, *o-* Ar-H adjacent to CCH_3). ν/cm^{-1} 2195 (C≡N), 1694 (C=O), 1655 (C=O). See Appendix 10 (page 200) for details of X-ray structure analysis.



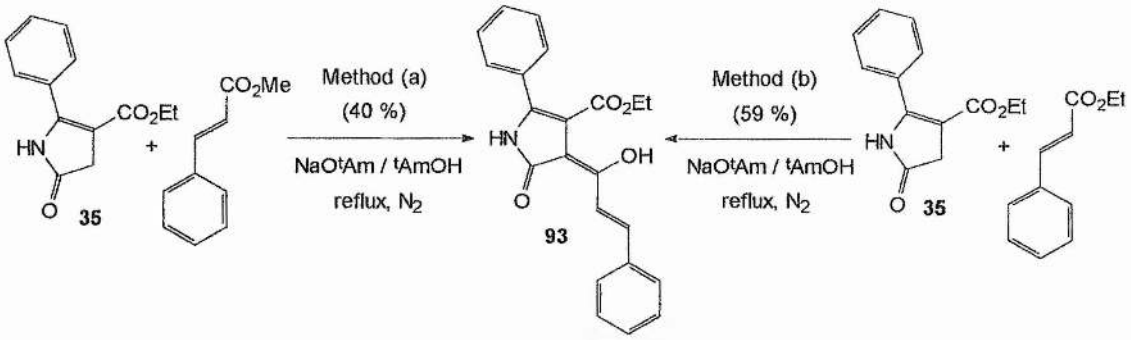
91 (10 %)

Reaction of the lactam ester 35 with α-phenylcinnamonitrile to yield 91

To pre-dried *t*-amyl alcohol (180 ml) was added sodium (7.0 g, 0.3045 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (23.5 g, 0.1016 mol) and α-phenylcinnamonitrile (20.86 g, 0.1016 mol) were then added and the mixture was heated to reflux for 6 h. The mixture was cooled then added to an ice-cooled mixture of water (200 ml) and methanol (50 ml) then acidified dropwise with concentrated hydrochloric acid. The purple precipitate was filtered off, washed with methanol and

water, then dried *in vacuo*. Yield 3.92 g (10 %). ν/cm^{-1} 3130 (weak, NH), 1635 (C=O). (A sufficiently pure sample was not readily prepared due to the low solubility of this material; found: C, 70.5; H, 4.0; N, 6.7 %. $C_{26}H_{18}N_2O_2$ requires C, 80.0, H, 4.7; N, 7.2 %). *m/z* 390.1354 ($M^{+\cdot}$, 5 %, $C_{26}H_{18}N_2O_2$ requires 390.1368), 319 (100), 230 (67), 115 (15), 77 (22).

6.5 Experimental for Chapter 5

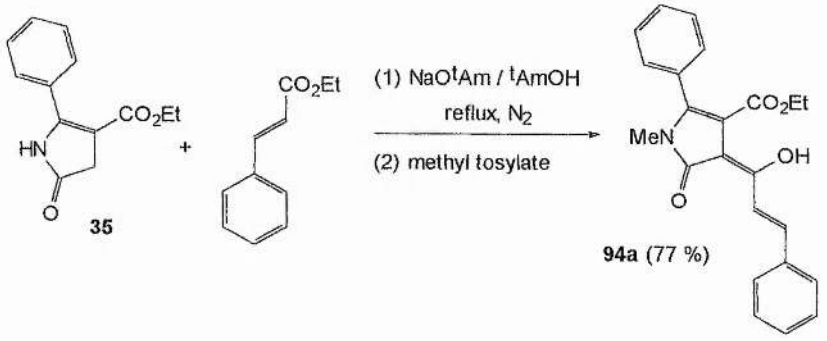


3-Cinnamoyl-4-ethoxycarbonyl-5-phenyl-4-pyrrolin-2-one 93

Method (a) To pre-dried *t*-amyl alcohol (25 ml) was added sodium (0.6 g, 0.0261 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The solution was cooled to 25 °C, then the lactam ester **35** (2.0 g, 0.0086 mol) and methyl cinnamate (1.40 g, 0.0086 mol) were added. The mixture was then heated to reflux for 2.5 h during which time an intense orange solution developed. The cooled mixture was added to an ice-cooled mixture of methanol (10 ml) and water (20 ml) then acidified dropwise with concentrated hydrochloric acid (3 ml). The orange precipitate was filtered off, washed with methanol and water then dried *in vacuo*. Yield 1.25 g (40 %).

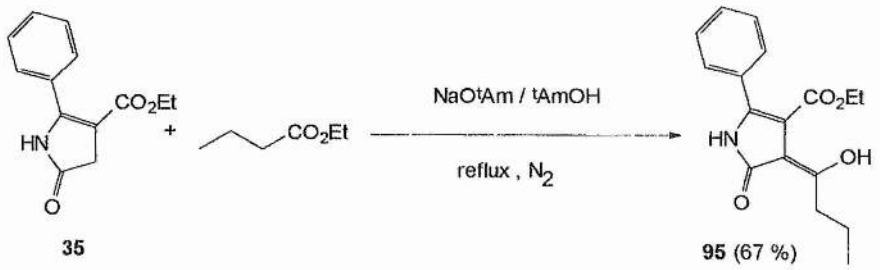
Method (b) To pre-dried *t*-amyl alcohol (70 ml) was added sodium (1.21 g, 0.0526 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (3.32 g, 0.0144 mol) and ethyl cinnamate (2.55 g, 0.0145 mol) were then added and the mixture was heated to reflux for 2 h. The cooled mixture was then added to an ice-cooled mixture of methanol (20 ml) and concentrated hydrochloric acid (5 ml) and the bright orange precipitate was filtered off, washed with methanol and dried in vacuo at 40 °C. Yield 3.05 g (59 %),

m.p. 238-240 °C. (Found: C, 72.8; H, 5.3; N, 3.8 % $C_{22}H_{19}NO_4$ requires C, 73.1, H, 5.3; N, 3.9 %). *m/z* 361 ($M^{+\cdot}$, 100 %), 315 (77), 238 (72). δ_H (DMSO-d_6) 0.88 (3H, t, OCH_2CH_3), 4.00 (2H, q, J 6.6, OCH_2CH_3), 7.43-7.47 (8H, m, Ar-H), 7.59 (1H, d, CH=CHPh),7.62-7.64 (2H, m, Ar-H), 8.62 (1H, d, J 15.7, CH=CHPh), 11.11 (1H, s, NH).



3-Cinnamoyl-4-ethoxycarbonyl-1-methyl-5-phenyl-4-pyrrolin-2-one 94a

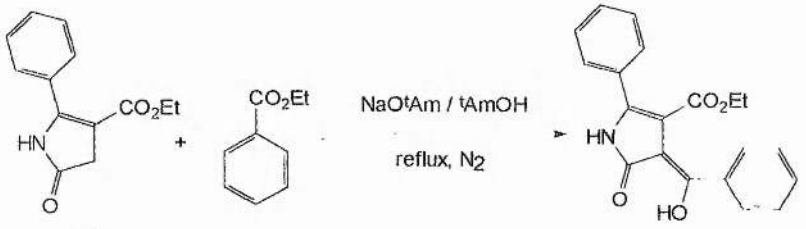
To pre-dried *t*-amyl alcohol (25 ml) was added sodium (1.51 g, 0.0657 mol) with stirring under nitrogen and the mixture was heated to reflux (105-110 °C) until all the sodium dissolved. The lactam ester **35** (5.0 g, 0.0216 mol) then ethyl cinnamate (3.88 g, 0.0220 mol) were then added and heating to reflux continued for 2 h during which time an orange coloured solution developed. The mixture was cooled to 25 °C, then methyl tosylate (15.88 g, 0.0853 mol) was added. Heating to reflux was continued for 1 h. The mixture was cooled, added to water (30 ml), extracted with ethyl acetate, dried (Na_2SO_4) then concentrated. Recrystallisation from propan-2-ol - tetrahydrofuran provided an orange solid. Yield 6.27 g (77 %), m.p. 190-192 °C. (Found: C, 73.4; H, 5.6; N, 3.7 % $C_{23}H_{21}NO_4$ requires C, 73.6, H, 5.6; N, 3.7 %). *m/z* (EI) 375 ($M^{+\cdot}$, 100%), 329 (98). δ_H (200 MHz) 0.75 (3H, t, J 7.2, OCH_2CH_3), 2.97 (3H, s, NCH_3), 3.97 (2H, q, OCH_2CH_3), 7.24-7.48 (8H, m, Ar-*H*), 7.67-7.76 (3H, m, Ar-*H* and CH=CHPh), 8.76-8.84 (1H, d, J 15.5, CH=CHPh). See Appendix 7 (page 181) for details of the X-ray structure analysis.



35 95 (67 %)

3-Butanoyl-4-ethoxycarbonyl-5-phenyl-4-pyrrolin-2-one 95

To pre-dried *t*-amyl alcohol (25 ml) was added sodium (0.61 g, 26.5 mmol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The solution was cooled to 80-90 °C, then the lactam ester **35** (2.0 g, 0.0086 mol) and ethyl butyrate (1.0 g, 8.6 mmol) were added. The mixture was then heated to reflux for 5 h. The cooled solution was added to an ice-cooled mixture of water (100 ml) and methanol (10 ml) then acidified dropwise with concentrated hydrochloric acid. The purple precipitate was filtered off then washed with methanol and water. The solid was dissolved in hot propan-2-ol, decolourised with activated charcoal and the solution then concentrated. Recrystallisation from dioxan yielded colourless crystals. Yield 1.74 g (67 %), m.p. 172-173 °C. (Found: C, 68.1; H, 6.6; N, 4.7. $C_{17}H_{19}NO_4$ requires C, 67.8, H, 6.4; N, 4.7 %). δ_H (DMSO-d_6) 0.91-0.96 (6H, m, OCH_2CH_3 + $CH_2CH_2CH_3$), 1.61 (2H, sextet, J 7.4, $CH_2CH_2CH_3$), 2.81-2.89 (2H, m, $CH_2CH_2CH_3$), 4.05 (2H, q, J 7.1, OCH_2CH_3), 7.39-7.42 (5H, m, Ar-H), 11.22 (1H, br. s, NH). See Appendix 8 (page 188) for details of the X-ray structure analysis.

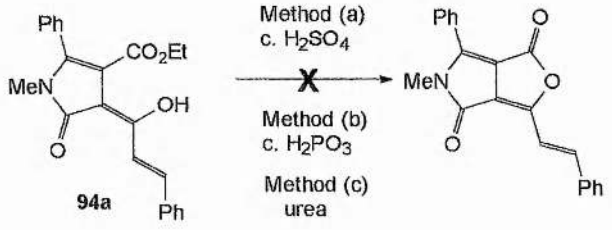


35 96 (33 %)

3-Benzoyl-4-ethoxycarbonyl-5-phenyl-4-pyrrolin-2-one 96

To pre-dried *t*-amyl alcohol (40 ml) was added sodium (1.50 g, 0.0652 mol) with stirring under nitrogen and the mixture heated to reflux (105-110 °C) until all the sodium dissolved. The solution was cooled to 25 °C, then the lactam ester **35** (5.03 g,

0.0218 mol) and ethyl benzoate (3.27 g, 0.0218 mol) were added. The mixture was then heated to reflux for 5.5 h during which time an orange solution developed. The cooled mixture was added to an ice-cooled mixture of methanol (10 ml) and water (50 ml), acidified dropwise with concentrated hydrochloric acid (3 ml) then extracted with tetrahydrofuran / diethyl ether, dried (Na_2SO_4) and concentrated. Recrystallisation from aqueous ethanol yielded amber coloured crystals. Yield 2.38 g (33 %), m.p. 156-157 °C. (Found: C, 71.5; H, 5.2; N, 4.2. $C_{20}H_{17}NO_4$ requires C, 71.6, H, 5.1; N, 4.2 %). δ_H 0.67 (3H, t, J 7.2, OCH_2CH_3), 3.56 (2H, q, OCH_2CH_3), 7.40-7.56 (6H, m, *m-/p-* Ar-H), 7.62-7.68 (4H, m, *o-* Ar-H), 9.52 (1H, br. s, NH). *m/z* 335 ($M^{+\cdot}$, 54 %), 289 (100), 105 (56). See Appendix 9 (page 194) for details of the X-ray structure analysis.

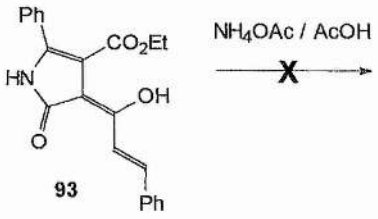


Attempted ring closure of compound 94a

Method (a) A small sample of compound **94a** was added to concentrated sulfuric acid. Upon gentle heating, the colour changed to bright orange. The mixture was added slowly to water, upon which an orange solid precipitated. This was filtered off, but only a tacky, intractable orange solid was recovered which was partly soluble in water.

Method (b). A small sample of compound **94a** (0.10 g, 0.3 mmol) was heated in a test tube with concentrated orthophosphoric acid. The mixture was then cooled and added to water, extracted with ethyl acetate then concentrated. No colour change was observed. ^{1}H NMR showed only unreacted starting material.

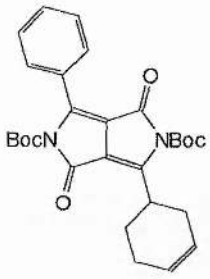
Method (c) A mixture of compound **94a** (0.10 g, 0.3 mmol) and urea (1.10 g, 18 mmol) was heated to 145 °C for 2 h. Water was then added, the mixture then extracted with ethyl acetate then concentrated and dried *in vacuo*. ^{1}H NMR showed only unreacted starting material **94a**.



Attempted ring closure of compound 93

A mixture of compound **93** (0.30 g, 0.8 mmol), ammonium acetate (3.07 g, 40 mmol) and acetic acid (15 ml) was heated to reflux under nitrogen for 4 h. The mixture was then added to ice-water and the orange-brown precipitate was filtered off, washed with water, then dried *in vacuo*. ^{1}H NMR showed only unreacted starting material **93**.

Appendix 1 — X-ray structure analysis



"The present "triclinic" data set (4696 refls) gives a very poor R_{int} (16%) on merging to yield a "monoclinic" data set with 2228 refls. The space group P2$_1$/c was chosen as being the best option (two cell angles are 90 degrees and the absences DO correspond with a monoclinic P2$_1$/c type cell).

The Z value of 2 in the cell DEMANDs that the molecule lie about an inversion centre and thus have the phenyl and cyclohexenyl moieties occupying the same site in the asymmetric unit.

The structure solved relatively easily with SHELXS-97. It was apparent at this "solution" stage that the phenyl/cyclohexenyl site had six peaks, some of which were distended normal to the plane. It was also obvious that the unique *t*-butoxy-carbonyl moiety was also disordered unequally over two sites.

All the disorder was successfully modelled using the available options in SHELXL-97. Using DFIX and Free-variable options, the geometry of the cyclohexenyl ring refined to yield a double-bond location consistent with what had been anticipated. The final model has the phenyl and cyclohexenyl rings (each with 0.5 occupancy) occupying the same volume element in the crystal lattice. The *t*-butoxy-carbonyl geometry was controlled by use of various DFIX options in SHELXL-97."

A. Crystal Data

Empirical Formula	C H N O
Formula Weight	492.57
Crystal Color, Habit	-
Crystal Dimensions/mm	-
Crystal System	monoclinic
Lattice Type	Primitive
a/Å	12.157(0)
b/Å	10.098(0)
c/Å	11.675(0)
α ( )	90
β ( )	117.63(0)
γ ( )	90
V/Å	1269.8(8)
Space Group	*P2 /c* (#14)
Z	1
F_{000}	524
D_{calc}/gcm	1.288
μ(MoKα)/cm^{-1}	0.091

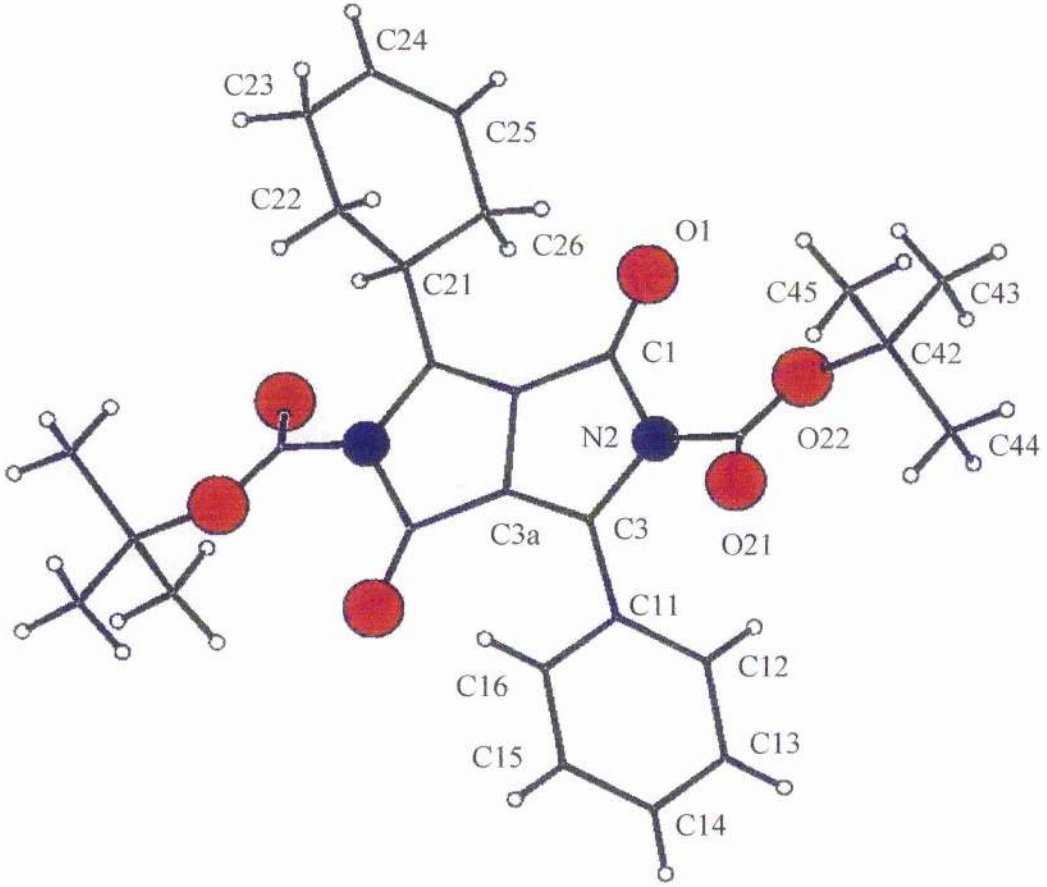
B. Data Aquisition

Max. 2θ ( ) for reflections	-
Reflections measured	4696
Reflections with $I > 2\sigma(I)$	2228

C. Structure solution & refinement

Solution method	SHELXS-97
No. of variables in LS	
R	0.0732
Density max in final ΔF-map (eÅ^{-})	0.435

Prof. George Ferguson
(University of Guelph, Canada)



Structure diagram with atom numbering scheme

Positional parameters (N.B./ centrosymmetric structure)

atom	x	y	z
O(1)	0.7627(2)	0.4687(3)	0.0606(3)
O(21)	0.6936(4)	0.2232(4)	0.2922(4)
O(22)	0.7923(3)	0.2214(4)	0.1698(4)
N(2)	0.6223(2)	0.3415(3)	0.1017(3)
C(1)	0.6592(3)	0.4521(3)	0.0486(4)
C(3)	0.4986(3)	0.3561(3)	0.0805(4)
C(3A)	0.4536(3)	0.4689(3)	0.0123(4)
C(11)	0.4335(3)	0.2559(3)	0.1188(4)
C(12)	0.4344(6)	0.1226(4)	0.0896(7)
C(13)	0.3612(9)	0.0331(4)	0.1144(10)
C(14)	0.2870(10)	0.0769(8)	0.1683(13)
C(15)	0.2861(11)	0.2103(10)	0.1975(14)
C(16)	0.3594(8)	0.2997(6)	0.1727(9)
C(21)	0.4335(3)	0.2559(3)	0.1188(4)
C(22)	0.3902(13)	0.1400(9)	0.0370(12)
C(23)	0.3299(14)	0.0354(13)	0.0744(14)
C(24)	0.2785(10)	0.0774(7)	0.1555(11)
C(25)	0.2810(8)	0.2041(11)	0.1930(11)
C(26)	0.3496(8)	0.3087(9)	0.1637(11)
C(31)	0.7058(4)	0.2502(4)	0.1906(5)
C(42)	0.9069(5)	0.1518(6)	0.2656(7)
C(43)	0.9749(5)	0.1348(5)	0.1882(5)
C(44)	0.8716(5)	0.0186(5)	0.2983(7)
C(45)	0.9751(6)	0.2360(6)	0.3825(6)
H(12)	0.48400	0.09320	0.05350
H(13)	0.36170	-0.05610	0.09480
H(14)	0.23800	0.01710	0.18490
H(15)	0.23650	0.23960	0.23360
H(16)	0.35880	0.38890	0.19230
H(21)	0.50090	0.21980	0.19830
H(22A)	0.46070	0.10120	0.03180
H(22B)	0.33220	0.16920	-0.04930
H(23A)	0.26430	-0.00300	-0.00340
H(23B)	0.39030	-0.03370	0.11860
H(24)	0.24110	0.01430	0.18410
H(25)	0.23830	0.22650	0.23880
H(26A)	0.29040	0.36710	0.09810
H(26B)	0.39670	0.36090	0.24100
H(43A)	0.92710	0.07970	0.11470
H(43B)	1.05380	0.09400	0.24080
H(43C)	0.98750	0.21980	0.15940
H(44A)	0.82810	-0.03220	0.22050
H(44B)	0.81900	0.03150	0.33830
H(44C)	0.94530	-0.02790	0.35670
H(45A)	0.92720	0.24390	0.42840
H(45B)	0.98830	0.32240	0.35670
H(45C)	1.05380	0.19610	0.43780

Intramolecular Distances (Å)

atom	atom	distance
O(1)	C(1)	1.211(5)
O(21)	C(31)	1.291(7)
O(22)	C(31)	1.448(10)
O(22)	C(42)	1.497(8)
N(2)	C(1)	1.446(5)
N(2)	C(3)	1.414(5)
N(2)	C(31)	1.407(6)
C(1)	C(3A)a	1.455(6)
C(3)	C(3A)	1.352(5)
C(3)	C(11)	1.476(5)
C(3)	C(21)	1.476(5)
C(3A)	C(3A)a	1.432(6)
C(11)	C(12)	1.390(5)
C(11)	C(16)	1.389(11)
C(12)	C(13)	1.390(12)
C(13)	C(14)	1.390(18)
C(14)	C(15)	1.391(13)
C(15)	C(16)	1.390(16)
C(21)	C(22)	1.447(11)
C(21)	C(26)	1.448(12)
C(22)	C(23)	1.46(2)
C(23)	C(24)	1.42(2)
C(24)	C(25)	1.348(14)
C(25)	C(26)	1.481(15)
C(42)	C(43)	1.491(10)
C(42)	C(44)	1.514(8)
C(42)	C(45)	1.491(9)

Selected Intramolecular Bond Angles (°)

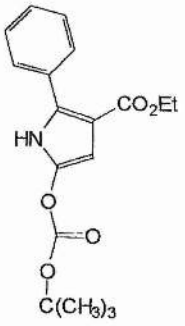
atom	atom	atom	angle
C21	C22	C23	117.8(11)
C22	C23	C24	114.8(10)
C23	C24	C25	123.3(8)
C24	C25	C26	122.2(7)
C21	C26	C25	112.8(8)
C3	C21	C26	115.1(4)
C3	C21	C22	115.9(7)
C22	C21	C26	115.8(8)

Selected Torsion or conformation angles (°)

atom	atom	atom	atom	angle
C22	C23	C24	C25	2(2)
C21	C22	C23	C24	23(2)
C23	C24	C25	C26	-7(2)
C24	C25	C26	C21	-13(2)
C23	C22	C21	C26	-43.3(14)

Appendix 2

X-ray structure analysis



A. Crystal Data

Empirical Formula	$C_{17}H_{21}NO_4$
Formula Weight	331.37
Crystal Color, Habit	colourless, plate
Crystal Dimensions/mm	0.50 × 0.30 × 0.08
Crystal System	monoclinic
Lattice Type	Primitive
a/Å	9.602(5)
b/Å	13.993(7)
c/Å	13.734(6)
α (°)	90
β (°)	104.42(4)
γ (°)	90
V/Å^3	1787(1)
Space Group	$P2_1/c$ (#14)
Z	4
F_{000}	704.00
D_{calc}/gcm^{-3}	1.231
μ(MoKα)/cm^{-1}	0.84

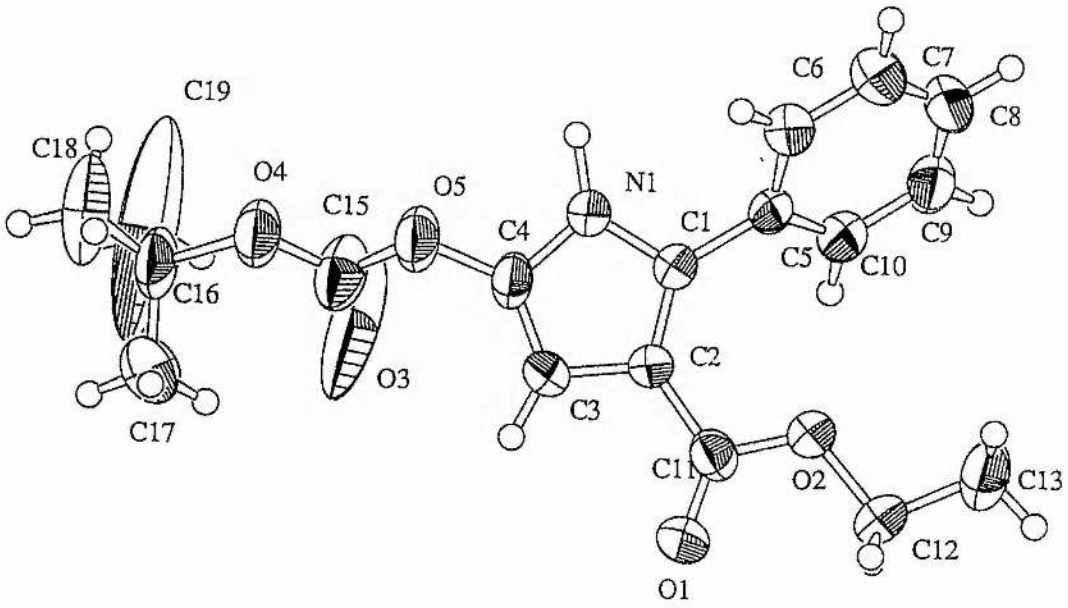
B. Data Acquisition

Max. 2θ (°) for reflections	50.0
Reflections measured	1831
Reflections with $I > 3\sigma(I)$	789

C. Structure solution and refinement

Solution method	Direct Methods (SIR92)
No. of variables in LS	223
R, Rw	0.083, 0.073
Density max in final ΔF-map (eÅ^{-3})	0.56

Dr. P. Lightfoot
University of St. Andrews



Structure diagram with atom numbering scheme

Positional parameters and B(eq)

atom	x	y	z	B(eq)
O(1)	0.9899(5)	0.4306(3)	0.1671(3)	5.9(1)
O(2)	0.8813(4)	0.3270(3)	0.0489(3)	4.3(1)
O(3)	1.3670(7)	0.2169(8)	0.4485(5)	18.4(3)
O(4)	1.3210(5)	0.1458(3)	0.5791(3)	5.7(1)
O(5)	1.1600(5)	0.1521(3)	0.4403(3)	6.3(1)
N(1)	1.0363(5)	0.1212(3)	0.2732(3)	4.0(1)
C(1)	0.9761(6)	0.1691(4)	0.1857(4)	3.5(1)
C(2)	1.0059(6)	0.2648(4)	0.2040(4)	3.5(1)
C(3)	1.0864(7)	0.2752(4)	0.3055(4)	4.1(2)
C(4)	1.1014(7)	0.1874(5)	0.3439(4)	4.4(2)
C(5)	0.8954(6)	0.1144(4)	0.0975(4)	3.7(1)
C(6)	0.7939(7)	0.0470(4)	0.1092(4)	4.8(2)
C(7)	0.7202(8)	-0.0063(5)	0.0272(6)	5.9(2)
C(8)	0.7456(8)	0.0080(5)	-0.0654(5)	6.3(2)
C(9)	0.8462(9)	0.0741(5)	-0.0778(5)	5.8(2)
C(10)	0.9204(7)	0.1268(4)	0.0039(5)	4.6(2)
C(11)	0.9606(6)	0.3485(4)	0.1404(4)	3.8(2)
C(12)	0.8329(7)	0.4068(4)	-0.0201(5)	4.8(2)
C(13)	0.7389(8)	0.3628(5)	-0.1138(5)	6.5(2)
C(15)	1.2928(8)	0.1766(6)	0.4880(6)	6.3(2)
C(16)	1.4540(9)	0.1693(6)	0.6562(6)	7.6(2)
C(17)	1.465(2)	0.2719(9)	0.658(1)	32.9(8)
C(18)	1.4307(9)	0.1299(8)	0.7489(6)	9.9(3)
C(19)	1.570(1)	0.122(2)	0.6313(8)	29.0(8)
H(1)	0.7751	0.0377	0.1732	5.7220
H(2)	0.6521	-0.0530	0.0353	7.0499
H(3)	0.6938	-0.0278	-0.1215	7.5193
H(4)	0.8647	0.0835	-0.1421	7.0055
H(5)	0.9898	0.1724	-0.0048	5.5009
H(6)	0.7796	0.4513	0.0084	5.8061
H(7)	0.9128	0.4382	-0.0351	5.8061
H(8)	0.6581	0.3332	-0.0980	7.8294
H(9)	0.7068	0.4111	-0.1628	7.8294
H(10)	0.7923	0.3163	-0.1395	7.8294
H(13)	1.5495	0.2919	0.7046	38.8907
H(14)	1.4565	0.2971	0.5948	38.8907
H(15)	1.3833	0.2970	0.6836	38.8907
H(16)	1.3503	0.1602	0.7642	11.8859
H(17)	1.4131	0.0631	0.7409	11.8859
H(18)	1.5138	0.1404	0.8022	11.8859
H(19)	1.5541	0.0544	0.6322	34.7318
H(20)	1.5743	0.1401	0.5654	34.7318
H(21)	1.6565	0.1375	0.6779	34.7318
H(22)	1.118(6)	0.337(4)	0.337(4)	5.9520
H(23)	1.027(6)	0.048(4)	0.292(4)	5.9520

Intramolecular Distances (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(11)	1.217(6)	C(2)	C(11)	1.462(7)
O(2)	C(11)	1.333(6)	C(3)	C(4)	1.331(8)
O(2)	C(12)	1.464(6)	C(5)	C(6)	1.394(8)
O(3)	C(15)	1.145(8)	C(5)	C(10)	1.375(8)
O(4)	C(15)	1.287(7)	C(6)	C(7)	1.389(8)
O(4)	C(16)	1.479(7)	C(7)	C(8)	1.367(9)
O(5)	C(4)	1.393(6)	C(8)	C(9)	1.38(1)
O(5)	C(15)	1.326(8)	C(9)	C(10)	1.383(8)
N(1)	C(1)	1.371(7)	C(12)	C(13)	1.507(8)
N(1)	C(4)	1.375(7)	C(16)	C(17)	1.44(1)
C(1)	C(2)	1.379(7)	C(16)	C(18)	1.46(1)
C(1)	C(5)	1.479(7)	C(16)	C(19)	1.40(2)
C(2)	C(3)	1.423(7)			

Intramolecular Bond Angles (°)

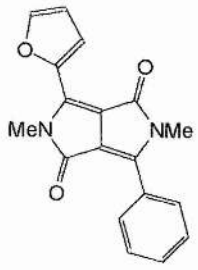
atom	atom	atom	angle	atom	atom	atom	angle
C(11)	O(2)	C(12)	116.9(5)	C(6)	C(7)	C(8)	120.1(7)
C(15)	O(4)	C(16)	123.8(6)	C(7)	C(8)	C(9)	120.4(7)
C(4)	O(5)	C(15)	119.3(5)	C(8)	C(9)	C(10)	119.5(7)
C(1)	N(1)	C(4)	108.0(5)	C(5)	C(10)	C(9)	121.1(6)
N(1)	C(1)	C(2)	107.0(5)	O(1)	C(11)	O(2)	122.2(6)
N(1)	C(1)	C(5)	119.1(5)	O(1)	C(11)	C(2)	124.4(5)
C(2)	C(1)	C(5)	133.9(5)	O(2)	C(11)	C(2)	113.4(5)
C(1)	C(2)	C(3)	108.4(5)	O(2)	C(12)	C(13)	105.5(5)
C(1)	C(2)	C(11)	130.7(5)	O(3)	C(15)	O(4)	128.4(7)
C(3)	C(2)	C(11)	120.8(5)	O(3)	C(15)	O(5)	121.9(7)
C(2)	C(3)	C(4)	105.8(5)	O(4)	C(15)	O(5)	109.7(6)
O(5)	C(4)	N(1)	115.9(5)	O(4)	C(16)	C(17)	106.5(8)
O(5)	C(4)	C(3)	133.0(6)	O(4)	C(16)	C(18)	104.4(6)
N(1)	C(4)	C(3)	110.9(5)	O(4)	C(16)	C(19)	108.4(9)
C(1)	C(5)	C(6)	119.6(5)	C(17)	C(16)	C(18)	113(1)
C(1)	C(5)	C(10)	121.5(6)	C(17)	C(16)	C(19)	114(1)
C(6)	C(5)	C(10)	118.9(6)	C(18)	C(16)	C(19)	109.7(9)
C(5)	C(6)	C(7)	120.0(6)				

Torsion or Conformation Angles (°)

(1)	(2)	(3)	(4)	angle
O(1)	C(11)	O(2)	C(12)	1.5(9)
O(1)	C(11)	C(2)	C(1)	176.9(7)
O(1)	C(11)	C(2)	C(3)	2(1)
O(2)	C(11)	C(2)	C(1)	-2(1)
O(2)	C(11)	C(2)	C(3)	-177.4(5)
O(3)	C(15)	O(4)	C(16)	9(2)
O(3)	C(15)	O(5)	C(4)	-9(1)
O(4)	C(15)	O(5)	C(4)	172.9(6)
O(5)	C(4)	N(1)	C(1)	175.7(5)
O(5)	C(4)	C(3)	C(2)	-174.8(7)
O(5)	C(15)	O(4)	C(16)	-173.3(7)
N(1)	C(1)	C(2)	C(3)	0.0(7)
N(1)	C(1)	C(2)	C(11)	-175.5(6)
N(1)	C(1)	C(5)	C(6)	47.0(8)
N(1)	C(1)	C(5)	C(10)	-131.4(6)
N(1)	C(4)	O(5)	C(15)	131.8(7)
N(1)	C(4)	C(3)	C(2)	0.3(8)
C(1)	N(1)	C(4)	C(3)	-0.4(8)
C(1)	C(2)	C(3)	C(4)	-0.2(8)
C(1)	C(5)	C(6)	C(7)	-178.4(6)
C(1)	C(5)	C(10)	C(9)	178.8(6)
C(2)	C(1)	N(1)	C(4)	0.2(7)
C(2)	C(1)	C(5)	C(6)	-131.2(7)
C(2)	C(1)	C(5)	C(10)	50(1)
C(2)	C(11)	O(2)	C(12)	-179.2(5)
C(3)	C(2)	C(1)	C(5)	178.4(6)
C(3)	C(4)	O(5)	C(15)	-53(1)
C(4)	N(1)	C(1)	C(5)	-178.4(5)
C(4)	C(3)	C(2)	C(11)	175.8(6)
C(5)	C(1)	C(2)	C(11)	3(1)
C(5)	C(6)	C(7)	C(8)	-1(1)
C(5)	C(10)	C(9)	C(8)	0(1)
C(6)	C(5)	C(10)	C(9)	0.4(9)
C(6)	C(7)	C(8)	C(9)	1(1)
C(7)	C(6)	C(5)	C(10)	0.1(9)
C(7)	C(8)	C(9)	C(10)	-1(1)
C(11)	O(2)	C(12)	C(13)	-176.3(5)
C(15)	O(4)	C(16)	C(17)	53(2)
C(15)	O(4)	C(16)	C(18)	172.8(8)
C(15)	O(4)	C(16)	C(19)	-70(1)

Appendix 3

X-ray structure analysis



A. Crystal Data

Empirical Formula	$C_{17}H_{15}NO_3$
Formula Weight	306.32
Crystal Color, Habit	red, block
Crystal Dimensions/mm	0.35 × 0.35 × 0.10
Crystal System	monoclinic
Lattice Type	Primitive
a/Å	18.421(6)
b/Å	11.607(3)
c/Å	7.003(1)
α (°)	90
β (°)	100.94(2)
γ (°)	90
V/Å^3	1470.1(6)
Space Group	$P2_1/n$(#14)
Z	4
F_{000}	640.00
D_{calc}/gcm^{-3}	1.384
μ(MoKα)/cm^{-1}	0.96

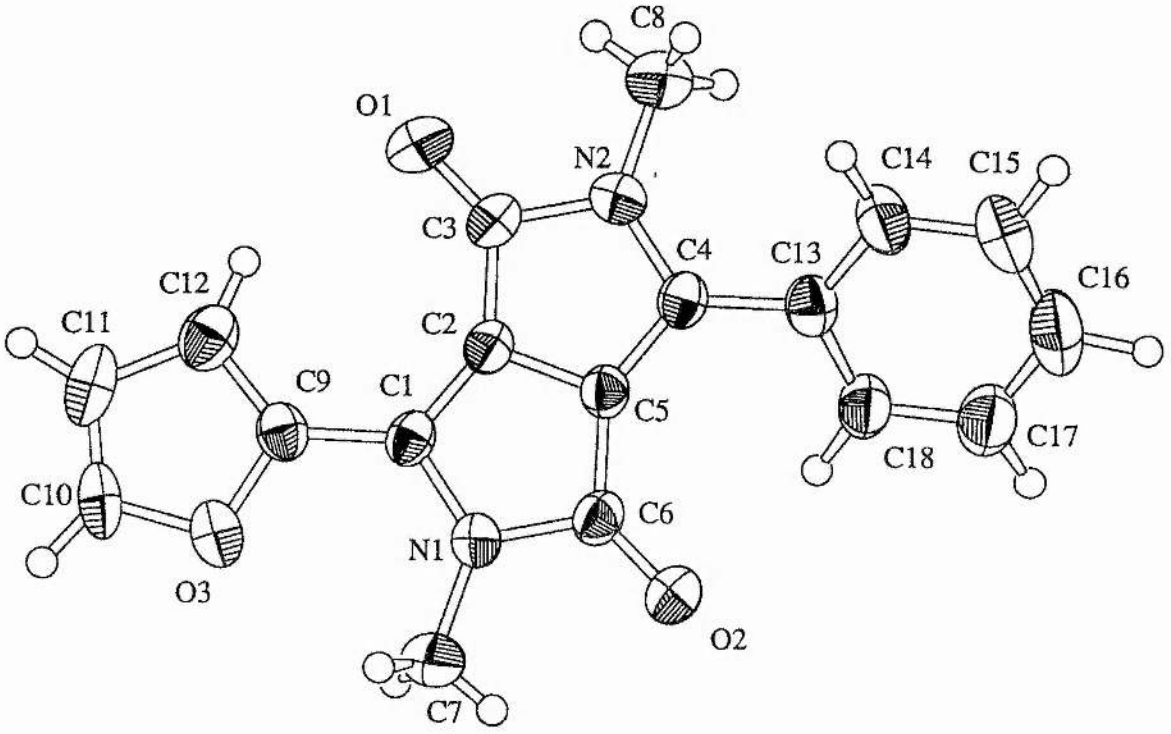
B. Data Acquisition

Max. 2θ ( ) for reflections	45.0
Reflections measured	2090
Reflections with $I > 3\sigma(I)$	1219

C. Structure solution and refinement

Solution method	Direct Methods (SIR92)
No. of variables in LS	250
R, Rw	0.052, 0.070
Density max in final ΔF-map (eÅ^{-3})	0.40

Dr. P. Lightfoot
University of St. Andrews



Structure diagram with atom numbering scheme

Positional parameters and B(eq)

atom	x	y	z	B(eq)
O(1)	0.9669(2)	0.2180(3)	0.6368(5)	4.91(9)
O(2)	0.7981(2)	-0.2133(3)	0.6327(5)	4.73(9)
O(3)	1.0793(2)	-0.1570(3)	0.8949(5)	4.06(8)
N(1)	0.9212(2)	-0.1632(3)	0.7333(5)	3.21(9)
N(2)	0.8439(2)	0.1671(3)	0.5278(5)	3.56(10)
C(1)	0.9640(2)	-0.0652(4)	0.7385(6)	2.9(1)
C(2)	0.9188(2)	0.0232(4)	0.6595(6)	2.8(1)
C(3)	0.9193(2)	0.1450(4)	0.6140(7)	3.3(1)
C(4)	0.8009(2)	0.0692(4)	0.5229(6)	2.9(1)
C(5)	0.8462(2)	-0.0182(4)	0.6041(6)	2.9(1)
C(6)	0.8469(2)	-0.1404(4)	0.6500(6)	3.2(1)
C(7)	0.9435(3)	-0.2774(5)	0.8094(9)	5.0(2)
C(8)	0.8202(3)	0.2856(5)	0.487(1)	5.2(2)
C(9)	1.0423(2)	-0.0593(4)	0.8162(6)	3.1(1)
C(10)	1.1516(3)	-0.1255(6)	0.9541(7)	4.3(1)
C(11)	1.1605(3)	-0.0144(6)	0.9193(8)	4.7(1)
C(12)	1.0901(3)	0.0303(5)	0.8285(7)	4.0(1)
C(13)	0.7213(2)	0.0640(4)	0.4423(6)	3.4(1)
C(14)	0.6861(3)	0.1309(5)	0.2857(7)	4.4(1)
C(15)	0.6124(3)	0.1171(6)	0.2142(8)	5.1(2)
C(16)	0.5723(3)	0.0379(6)	0.2913(9)	5.7(2)
C(17)	0.6054(3)	-0.0297(5)	0.4464(9)	5.1(2)
C(18)	0.6798(3)	-0.0162(4)	0.5195(8)	4.2(1)
H(1)	0.905(3)	-0.323(4)	0.799(7)	5.0000
H(2)	0.958(2)	-0.277(4)	0.949(7)	5.0000
H(3)	0.985(2)	-0.308(4)	0.730(7)	5.0000
H(4)	0.859(3)	0.334(4)	0.544(7)	5.0000
H(5)	0.815(2)	0.393(4)	0.340(7)	5.0000
H(6)	0.775(3)	0.296(4)	0.520(7)	5.0000
H(7)	1.164(2)	-0.183(4)	1.018(7)	5.0000
H(8)	1.205(2)	0.025(4)	0.941(6)	5.0000
H(9)	1.270(3)	0.105(4)	0.787(7)	5.0000
H(10)	0.719(2)	0.179(4)	0.709(7)	5.0000
H(11)	0.589(3)	0.169(4)	0.111(7)	5.0000
H(12)	0.516(3)	0.023(4)	0.252(6)	5.0000
H(13)	0.573(3)	-0.077(4)	0.505(7)	5.0000
H(14)	0.703(3)	-0.065(4)	0.634(7)	5.0000

Intramolecular Distances (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(3)	1.208(5)	C(2)	C(5)	1.405(5)
O(2)	C(6)	1.224(5)	C(4)	C(5)	1.366(5)
O(3)	C(9)	1.383(5)	C(4)	C(13)	1.470(6)
O(3)	C(10)	1.367(5)	C(5)	C(6)	1.454(6)
N(1)	C(1)	1.382(5)	C(9)	C(12)	1.355(6)
N(1)	C(6)	1.407(5)	C(10)	C(11)	1.328(7)
N(1)	C(7)	1.458(6)	C(11)	C(12)	1.430(7)
N(2)	C(3)	1.429(5)	C(13)	C(14)	1.399(6)
N(2)	C(4)	1.382(5)	C(13)	C(18)	1.378(6)
N(2)	C(8)	1.454(6)	C(14)	C(15)	1.364(7)
C(1)	C(2)	1.371(6)	C(15)	C(16)	1.354(8)
C(1)	C(9)	1.442(6)	C(16)	C(17)	1.384(8)
C(2)	C(3)	1.450(6)	C(17)	C(18)	1.377(7)

Intramolecular Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(9)	O(3)	C(10)	106.3(4)	C(2)	C(5)	C(6)	107.7(4)
C(1)	N(1)	C(6)	111.2(3)	C(4)	C(5)	C(6)	142.7(4)
C(1)	N(1)	C(7)	128.2(4)	O(2)	C(6)	N(1)	123.3(4)
C(6)	N(1)	C(7)	120.5(4)	O(2)	C(6)	C(5)	132.6(4)
C(3)	N(2)	C(4)	111.7(3)	N(1)	C(6)	C(5)	104.0(3)
C(3)	N(2)	C(8)	119.0(4)	O(3)	C(9)	C(1)	119.6(4)
C(4)	N(2)	C(8)	128.6(4)	O(3)	C(9)	C(12)	109.8(4)
N(1)	C(1)	C(2)	107.8(3)	C(1)	C(9)	C(12)	130.6(4)
N(1)	C(1)	C(9)	125.0(4)	O(3)	C(10)	C(11)	110.6(5)
C(2)	C(1)	C(9)	127.2(4)	C(10)	C(11)	C(12)	107.5(5)
C(1)	C(2)	C(3)	142.2(4)	C(9)	C(12)	C(11)	105.9(5)
C(1)	C(2)	C(5)	109.2(4)	C(4)	C(13)	C(14)	123.9(4)
C(3)	C(2)	C(5)	108.6(4)	C(4)	C(13)	C(18)	117.7(4)
O(1)	C(3)	N(2)	123.6(4)	C(14)	C(13)	C(18)	118.3(4)
O(1)	C(3)	C(2)	133.6(4)	C(13)	C(14)	C(15)	120.2(5)
N(2)	C(3)	C(2)	102.8(3)	C(14)	C(15)	C(16)	120.9(6)
N(2)	C(4)	C(5)	107.4(3)	C(15)	C(16)	C(17)	120.3(5)
N(2)	C(4)	C(13)	124.6(4)	C(16)	C(17)	C(18)	119.1(6)
C(5)	C(4)	C(13)	128.0(4)	C(13)	C(18)	C(17)	121.2(5)
C(2)	C(5)	C(4)	109.5(4)				

Torsion or Conformation Angles (°)

(1)	(2)	(3)	(4)	angle
O(1)	C(3)	N(2)	C(4)	-178.8(4)
O(1)	C(3)	N(2)	C(8)	-8.0(7)
O(1)	C(3)	C(2)	C(1)	-1(1)
O(1)	C(3)	C(2)	C(5)	178.3(5)
O(2)	C(6)	N(1)	C(1)	-178.7(4)
O(2)	C(6)	N(1)	C(7)	-1.6(7)
O(2)	C(6)	C(5)	C(2)	178.6(5)
O(2)	C(6)	C(5)	C(4)	-4(1)
O(3)	C(9)	C(1)	N(1)	-0.7(7)
O(3)	C(9)	C(1)	C(2)	178.5(4)
O(3)	C(9)	C(12)	C(11)	0.1(5)
O(3)	C(10)	C(11)	C(12)	-1.0(6)
N(1)	C(1)	C(2)	C(3)	179.7(5)
N(1)	C(1)	C(2)	C(5)	0.3(5)
N(1)	C(1)	C(9)	C(12)	179.5(4)
N(1)	C(6)	C(5)	C(2)	0.7(5)
N(1)	C(6)	C(5)	C(4)	178.5(6)
N(2)	C(3)	C(2)	C(1)	179.5(6)
N(2)	C(3)	C(2)	C(5)	-1.1(5)
N(2)	C(4)	C(5)	C(2)	-0.7(5)
N(2)	C(4)	C(5)	C(6)	-178.5(6)
N(2)	C(4)	C(13)	C(14)	32.3(7)
N(2)	C(4)	C(13)	C(18)	-151.4(4)
C(1)	N(1)	C(6)	C(5)	-0.5(5)
C(1)	C(2)	C(5)	C(4)	-179.2(4)
C(1)	C(2)	C(5)	C(6)	-0.7(5)

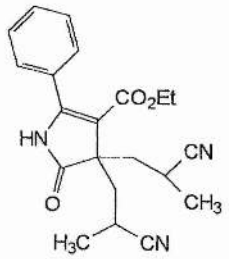
(1)	(2)	(3)	(4)	angle
C(1)	C(9)	O(3)	C(10)	179.5(4)
C(1)	C(9)	C(12)	C(11)	179.9(5)
C(2)	C(1)	N(1)	C(6)	0.1(5)
C(2)	C(1)	N(1)	C(7)	-176.6(5)
C(2)	C(1)	C(9)	C(12)	-1.2(8)
C(2)	C(3)	N(2)	C(4)	0.8(5)
C(2)	C(3)	N(2)	C(8)	171.5(5)
C(2)	C(5)	C(4)	C(13)	178.9(4)
C(3)	N(2)	C(4)	C(5)	-0.1(5)
C(3)	N(2)	C(4)	C(13)	-179.7(4)
C(3)	C(2)	C(1)	C(9)	0.3(9)
C(3)	C(2)	C(5)	C(4)	1.2(5)
C(3)	C(2)	C(5)	C(6)	179.8(4)
C(4)	C(13)	C(14)	C(15)	177.1(5)
C(4)	C(13)	C(18)	C(17)	-177.2(5)
C(5)	C(2)	C(1)	C(9)	-179.0(4)
C(5)	C(4)	N(2)	C(8)	-169.7(5)
C(5)	C(4)	C(13)	C(14)	-147.3(5)
C(5)	C(4)	C(13)	C(18)	29.1(7)
C(5)	C(6)	N(1)	C(7)	176.5(4)
C(6)	N(1)	C(1)	C(9)	179.5(4)
C(6)	C(5)	C(4)	C(13)	1.2(9)
C(7)	N(1)	C(1)	C(9)	-2.7(8)
C(8)	N(2)	C(4)	C(13)	10.6(7)
C(9)	O(3)	C(10)	C(11)	1.0(6)
C(9)	C(12)	C(11)	C(10)	-0.9(6)

Torsion or Conformation Angles (°) (continued)

(1)	(2)	(3)	(4)	angle
C(10)	O(3)	C(9)	C(12)	-0.7(5)
C(13)	C(14)	C(15)	C(16)	-0.8(9)
C(13)	C(18)	C(17)	C(16)	0.7(8)
C(14)	C(13)	C(18)	C(17)	-0.7(7)
C(14)	C(15)	C(16)	C(17)	0.8(9)
C(15)	C(14)	C(13)	C(18)	0.7(7)
C(15)	C(16)	C(17)	C(18)	-0.7(8)

Appendix 4

X-ray structure analysis



A. Crystal Data

Empirical Formula	$C_{21}H_{19}N_3O_3$
Formula Weight	365.43
Crystal Color, Habit	orange, plate
Crystal Dimensions/mm	0.40 × 0.10 × 0.02
Crystal System	monoclinic
Lattice Type	Primitive
a/Å	10.844(6)
b/Å	14.246(4)
c/Å	13.658(6)
α ( )	90
β ( )	105.58(3)
γ ( )	90
V/Å	2032(1)
Space Group	$P2_1/n$ (#14)
Z	4
F_{000}	776.00
D_{calc}/gcm^{-3}	1.194
$\mu(MoK\alpha)/cm^{-1}$	0.81

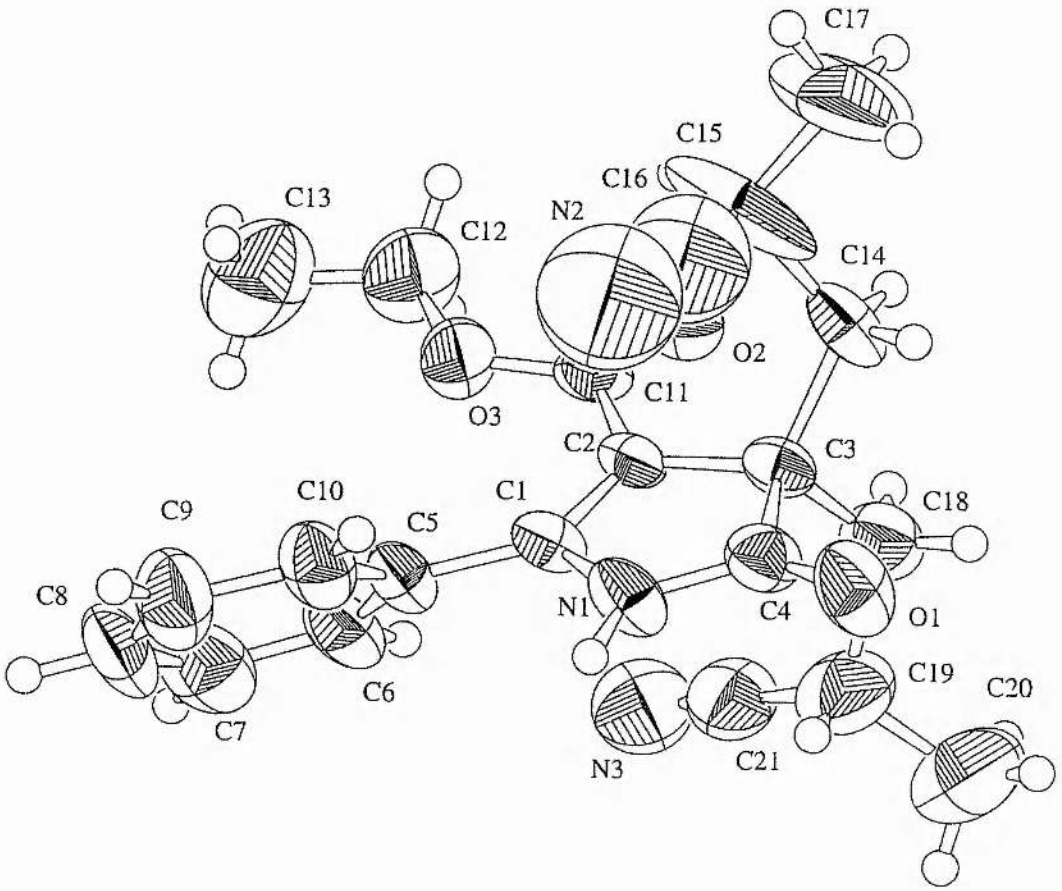
B. Data Acquisition

Max. 2θ ( ) for reflections	40.0
Reflections measured	1950
Reflections with $I > 3\sigma(I)$	1147

C. Structure solution and refinement

Solution method	direct methods (SIR92)
No. of variables in LS	234
R, wR	0.097, 0.09%
Density max in final ΔF-map (eÅ)	0.89

Dr. P. Lightfoot
University of St. Andrews



Structure diagram with atom numbering scheme

Positional parameters and B(eq)

atom	x	y	z	B(eq)
O(1)	0.0674(9)	0.1948(5)	0.8881(7)	5.8(3)
O(2)	0.2466(8)	-0.0850(5)	0.6988(6)	5.8(3)
O(3)	0.4196(10)	0.0001(5)	0.6988(6)	5.2(3)
N(1)	0.237(1)	0.2138(6)	0.8166(7)	4.3(3)
N(2)	0.401(2)	0.125(1)	1.048(1)	16.5(7)
N(3)	0.112(1)	0.1067(9)	0.5042(10)	7.6(4)
C(1)	0.306(1)	0.1594(8)	0.7647(8)	3.5(3)
C(2)	0.258(1)	0.0708(8)	0.7564(8)	3.5(4)
C(3)	0.144(1)	0.0659(7)	0.7994(8)	3.4(3)
C(4)	0.142(1)	0.1664(8)	0.8430(9)	4.3(4)
C(5)	0.408(1)	0.2030(7)	0.732(1)	3.7(4)
C(6)	0.415(1)	0.1972(8)	0.633(1)	5.1(4)
C(7)	0.509(2)	0.240(1)	0.600(1)	6.7(5)
C(8)	0.603(2)	0.2893(10)	0.669(2)	7.3(6)
C(9)	0.599(2)	0.2969(9)	0.769(1)	6.9(5)
C(10)	0.499(2)	0.2552(9)	0.801(1)	5.2(4)
C(11)	0.307(1)	-0.0108(8)	0.7155(8)	4.0(4)
C(12)	0.473(2)	-0.0772(10)	0.658(1)	6.9(5)
C(13)	0.593(2)	-0.048(1)	0.642(1)	9.8(6)
C(14)	0.153(1)	-0.0084(7)	0.8858(9)	5.0(4)
C(15)	0.295(2)	-0.0287(10)	0.958(1)	11.6(6)
C(16)	0.337(2)	0.052(2)	1.004(2)	12.8(6)
C(17)	0.269(2)	-0.084(1)	1.050(1)	13.2(7)
C(18)	0.016(1)	0.0513(8)	0.721(1)	5.4(4)
C(19)	-0.021(2)	0.124(1)	0.633(1)	7.3(5)
C(20)	-0.159(2)	0.129(1)	0.585(1)	12.1(7)
C(21)	0.054(2)	0.113(1)	0.562(1)	6.0(5)
H(1)	0.3520	0.1620	0.5852	6.1225
H(2)	0.5094	0.2356	0.5310	8.0249
H(3)	0.6706	0.3182	0.6479	8.7319
H(4)	0.6645	0.3304	0.8171	8.3392
H(5)	0.4937	0.2627	0.8684	6.2202
H(6)	0.4163	-0.0963	0.5956	8.3095
H(7)	0.4871	-0.1282	0.7048	8.3095
H(8)	0.5789	0.0030	0.5951	11.7396
H(9)	0.6495	-0.0282	0.7046	11.7396
H(10)	0.6307	-0.0987	0.6152	11.7396
H(11)	0.1017	0.0132	0.9276	5.9804

Positional parameters and B(eq) (continued)

atom	x	y	z	B(eq)
H(12)	0.1195	-0.0660	0.8546	5.9804
H(13)	0.3519	-0.0588	0.9257	13.8672
H(14)	0.3468	-0.0917	1.1016	15.8147
H(15)	0.2099	-0.0497	1.0766	15.8147
H(16)	0.2339	-0.1438	1.0276	15.8147
H(17)	0.0180	-0.0089	0.6916	6.4298
H(18)	-0.0485	0.0526	0.7562	6.4298
H(19)	0.0019	0.1834	0.6642	8.7563
H(20)	-0.1759	0.1786	0.5367	14.4914
H(21)	-0.2028	0.1405	0.6353	14.4914
H(22)	-0.1874	0.0713	0.5517	14.4914
H(23)	0.2544	0.2784	0.8320	5.1151

Intramolecular Distances (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(4)	1.21(1)	C(3)	C(18)	1.52(2)
O(2)	C(11)	1.23(1)	C(5)	C(6)	1.38(1)
O(3)	C(11)	1.31(1)	C(5)	C(10)	1.38(1)
O(3)	C(12)	1.43(1)	C(6)	C(7)	1.35(2)
N(1)	C(1)	1.40(1)	C(7)	C(8)	1.39(2)
N(1)	C(4)	1.36(1)	C(8)	C(9)	1.38(2)
N(2)	C(16)	1.31(2)	C(9)	C(10)	1.40(2)
N(3)	C(21)	1.14(2)	C(12)	C(13)	1.44(2)
C(1)	C(2)	1.36(1)	C(14)	C(15)	1.62(2)
C(1)	C(5)	1.44(1)	C(15)	C(16)	1.32(2)
C(2)	C(3)	1.51(1)	C(15)	C(17)	1.57(2)
C(2)	C(11)	1.45(1)	C(18)	C(19)	1.55(2)
C(3)	C(4)	1.55(1)	C(19)	C(20)	1.47(2)
C(3)	C(14)	1.57(1)	C(19)	C(21)	1.43(2)

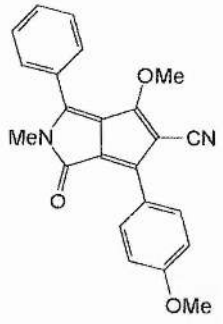
Intramolecular Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(11)	O(3)	C(12)	118(1)	C(5)	C(6)	C(7)	123(1)
C(1)	N(1)	C(4)	114.1(9)	C(6)	C(7)	C(8)	119(1)
N(1)	C(1)	C(2)	108(1)	C(7)	C(8)	C(9)	120(1)
N(1)	C(1)	C(5)	119(1)	C(8)	C(9)	C(10)	120(1)
C(2)	C(1)	C(5)	133(1)	C(5)	C(10)	C(9)	119(1)
C(1)	C(2)	C(3)	110(1)	O(2)	C(11)	O(3)	123(1)
C(1)	C(2)	C(11)	128(1)	O(2)	C(11)	C(2)	122(1)
C(3)	C(2)	C(11)	122(1)	O(3)	C(11)	C(2)	115(1)
C(2)	C(3)	C(4)	102(1)	O(3)	C(12)	C(13)	108(1)
C(2)	C(3)	C(14)	116(1)	C(3)	C(14)	C(15)	116(1)
C(2)	C(3)	C(18)	115(1)	C(14)	C(15)	C(16)	107(2)
C(4)	C(3)	C(14)	109.7(9)	C(14)	C(15)	C(17)	103(1)
C(4)	C(3)	C(18)	107(1)	C(16)	C(15)	C(17)	100(2)
C(14)	C(3)	C(18)	107(1)	N(2)	C(16)	C(15)	169(2)
O(1)	C(4)	N(1)	129(1)	C(3)	C(18)	C(19)	117(1)
O(1)	C(4)	C(3)	126(1)	C(18)	C(19)	C(20)	114(1)
N(1)	C(4)	C(3)	105(1)	C(18)	C(19)	C(21)	112(1)
C(1)	C(5)	C(6)	122(1)	C(20)	C(19)	C(21)	113(1)
C(1)	C(5)	C(10)	119(1)	N(3)	C(21)	C(19)	179(2)
C(6)	C(5)	C(10)	119(1)				

Torsion or Conformation Angles (°)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
O(1)	C(4)	N(1)	C(1)	180(1)	C(2)	C(1)	N(1)	C(4)	-1(1)
O(1)	C(4)	C(3)	C(2)	-178(1)	C(2)	C(1)	C(5)	C(6)	53(2)
O(1)	C(4)	C(3)	C(14)	-55(2)	C(2)	C(1)	C(5)	C(10)	-130(1)
O(1)	C(4)	C(3)	C(18)	61(2)	C(2)	C(3)	C(14)	C(15)	32(1)
O(2)	C(11)	O(3)	C(12)	1(2)	C(2)	C(3)	C(18)	C(19)	-56(1)
O(2)	C(11)	C(2)	C(1)	-170(1)	C(2)	C(11)	O(3)	C(12)	-180(1)
O(2)	C(11)	C(2)	C(3)	11(2)	C(3)	C(2)	C(1)	C(5)	-177(1)
O(3)	C(11)	C(2)	C(1)	11(2)	C(3)	C(14)	C(15)	C(16)	62(2)
O(3)	C(11)	C(2)	C(3)	-168(1)	C(3)	C(14)	C(15)	C(17)	166(1)
N(1)	C(1)	C(2)	C(3)	4(1)	C(3)	C(18)	C(19)	C(20)	-158(1)
N(1)	C(1)	C(2)	C(11)	-175(1)	C(3)	C(18)	C(19)	C(21)	72(2)
N(1)	C(1)	C(5)	C(6)	-128(1)	C(4)	N(1)	C(1)	C(5)	179(1)
N(1)	C(1)	C(5)	C(10)	50(2)	C(4)	C(3)	C(2)	C(11)	174(1)
N(1)	C(4)	C(3)	C(2)	4(1)	C(4)	C(3)	C(14)	C(15)	-83(1)
N(1)	C(4)	C(3)	C(14)	127(1)	C(4)	C(3)	C(18)	C(19)	56(2)
N(1)	C(4)	C(3)	C(18)	-117(1)	C(5)	C(1)	C(2)	C(11)	5(2)
N(2)	C(16)	C(15)	C(14)	-145(11)	C(5)	C(6)	C(7)	C(8)	1(2)
N(2)	C(16)	C(15)	C(17)	108(11)	C(5)	C(10)	C(9)	C(8)	3(2)
N(3)	C(21)	C(19)	C(18)	-177(77)	C(6)	C(5)	C(10)	C(9)	-3(2)
N(3)	C(21)	C(19)	C(20)	52(78)	C(6)	C(7)	C(8)	C(9)	-2(2)
C(1)	N(1)	C(4)	C(3)	-2(1)	C(7)	C(6)	C(5)	C(10)	1(2)
C(1)	C(2)	C(3)	C(4)	-5(1)	C(7)	C(8)	C(9)	C(10)	-1(2)
C(1)	C(2)	C(3)	C(14)	-124(1)	C(11)	O(3)	C(12)	C(13)	177(1)
C(1)	C(2)	C(3)	C(18)	110(1)	C(11)	C(2)	C(3)	C(14)	95(1)
C(1)	C(5)	C(6)	C(7)	176(1)	C(11)	C(2)	C(3)	C(18)	-71(1)
C(1)	C(5)	C(10)	C(9)	179(1)	C(14)	C(3)	C(18)	C(19)	171(1)
C(15)	C(14)	C(3)	C(18)	162(1)					

Appendix 5 X-ray structure analysis



Intensity data were recorded at 291(2) K with a Siemens SMART CCD diffractometer, using the microcrystal diffraction facility on station 9.8 of the Synchroton Radiation Source, CLRC Daresbury Laboratory. We acknowledge the provision of time on DARTS, the UK national synchrotron radiation service at the CLRC Daresbury Laboratory.

A. Crystal Data

Empirical Formula	C H N O
Formula Weight	370.39
Crystal Color, Habit	red
Crystal Dimensions/mm	-
Crystal System	monoclinic
Lattice Type	Primitive
a/Å	7.6276(11)
b/Å	10.7938(16)
c/Å	21.657(3)
α ( )	90
β ( )	90.401(3)
γ ( )	90
V/Å	1783.0(4)
Space Group	*P2 /n* (#14)
Z	4
F_{000}	776
D_{calc}/gcm	1.380
μ(MoKα)/cm $^{-1}$	0.93

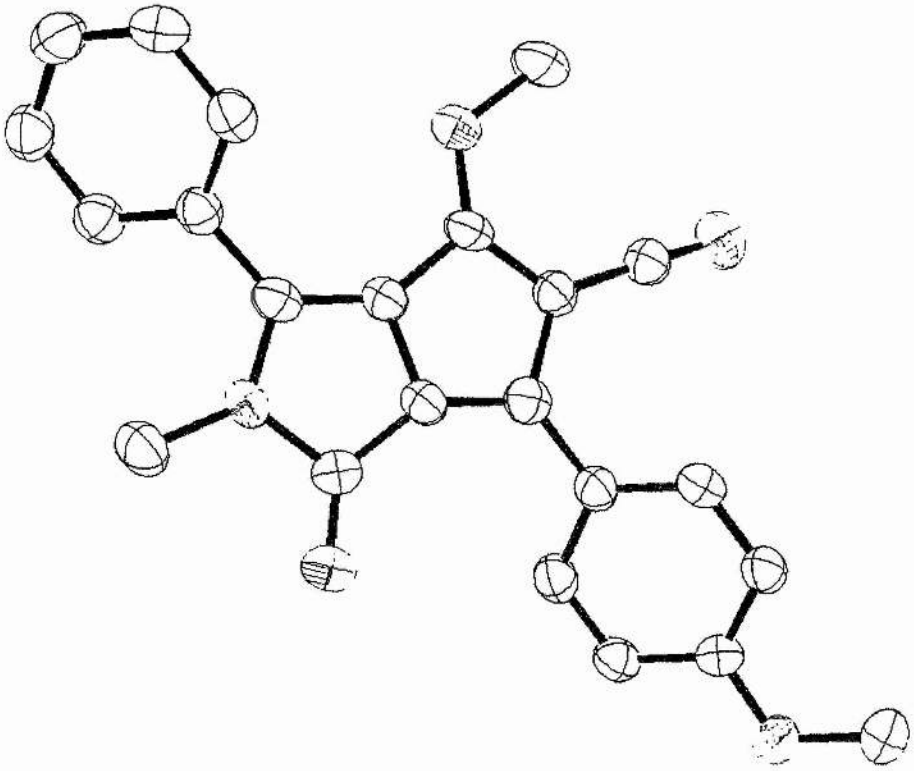
B. Data Acquisition

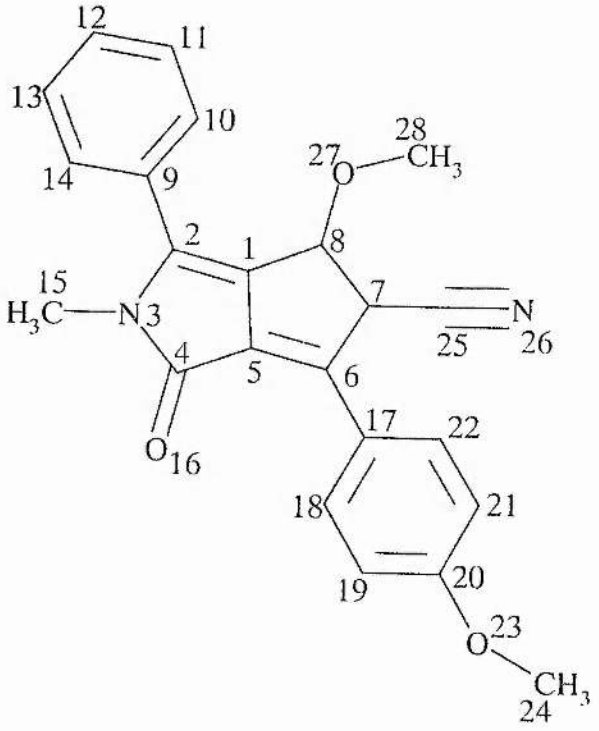
Max. 2θ ( ) for reflections	-
Reflections measured	6334
Reflections with $I > 2\sigma(I)$	1489

C. Structure solution and refinement

Solution method	direct methods
No. of variables in LS	-
R, Rw	0.0536, 0.1315
Density max in final ΔF-map (eÅ $^{-3}$)	0.305

Dr. E.J. Maclean
Daresbury Laboratory





Structure diagram with atom numbering scheme

Positional parameters and U_{eq}

	x	*y*	*z*	U(eq)
C(1)	7405(4)	4650(3)	5328.4(13)	37.8(8)
C(2)	6907(4)	5491(3)	5774.3(13)	37.1(8)
N(3)	6709(3)	6623(2)	5489.8(11)	40.5(7)
C(4)	7075(4)	6538(3)	4842.0(13)	41.2(8)
C(5)	7554(4)	5255(3)	4749.6(13)	38.8(8)
C(6)	8104(4)	4435(3)	4304.0(13)	37.8(8)
C(7)	8370(4)	3254(3)	4614.0(12)	35.8(8)
C(8)	7923(4)	3389(2)	5242.6(13)	37.1(8)
C(9)	6635(4)	5305(3)	6439.8(13)	36.6(7)
C(10)	5833(4)	4226(3)	6637.6(14)	42.5(8)
C(11)	5628(4)	4027(3)	7260.6(14)	47.9(9)
C(12)	6197(4)	4878(3)	7683.5(14)	49.5(9)
C(13)	6999(4)	5949(3)	7491.0(14)	48.6(9)
C(14)	7216(4)	6172(3)	6868.8(13)	41.5(8)
C(15)	5966(5)	7758(3)	5745.0(14)	52.6(9)
O(16)	6950(3)	7429(2)	4504.2(9)	58.6(7)
C(17)	8371(4)	4668(3)	3643.7(12)	36.3(7)
C(18)	8962(4)	5822(3)	3442.3(13)	40.8(8)
C(19)	9224(4)	6060(3)	2823.5(13)	40.0(8)
C(20)	8819(4)	5164(3)	2392.9(13)	39.3(8)
C(21)	8196(4)	4022(3)	2574.5(13)	40.0(8)
C(22)	7988(4)	3782(3)	3198.8(13)	38.5(8)
O(23)	9111(3)	5477(2)	1786.6(9)	55.3(7)
C(24)	8765(5)	4557(3)	1333.2(14)	62.3(11)
C(25)	9117(4)	2201(3)	4325.8(13)	42.0(8)
N(26)	9749(4)	1372(3)	4083.3(13)	61.0(9)
O(27)	7951(3)	2586(2)	5705.1(9)	48.6(6)
C(28)	8515(5)	1333(3)	5598.0(16)	67.9(12)

Intramolecular distances (Å)

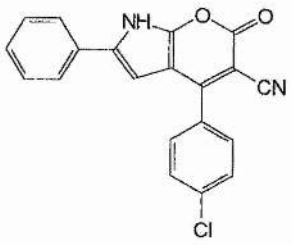
C(1)-C(2)	1.381(4)	C(1)-C(5)	1.419(4)	C(1)-C(8)	1.430(4)
C(2)-N(3)	1.376(3)	C(2)-C(9)	1.471(4)	N(3)-C(4)	1.435(4)
N(3)-C(15)	1.460(4)	C(4)-O(16)	1.212(3)	C(4)-C(5)	1.446(4)
C(5)-C(6)	1.378(4)	C(6)-C(7)	1.454(4)	C(6)-C(17)	1.468(4)
C(7)-C(8)	1.413(4)	C(7)-C(25)	1.418(4)	C(8)-O(27)	1.324(3)
C(9)-C(10)	1.385(4)	C(9)-C(14)	1.389(4)	C(10)-C(11)	1.376(4)
C(11)-C(12)	1.366(4)	C(12)-C(13)	1.375(4)	C(13)-C(14)	1.380(4)
C(17)-C(22)	1.387(4)	C(17)-C(18)	1.396(4)	C(18)-C(19)	1.380(4)
C(19)-C(20)	1.377(4)	C(20)-O(23)	1.376(3)	C(20)-C(21)	1.379(4)
C(21)-C(22)	1.387(4)	O(23)-C(24)	1.420(3)	C(25)-N(26)	1.146(4)
O(27)-C(28)	1.439(4)				

Intramolecular Bond Angles (°)

C(2)-C(1)-C(5)	109.8(2)	C(2)-C(1)-C(8)	142.6(3)
C(5)-C(1)-C(8)	107.4(2)	N(3)-C(2)-C(1)	107.5(2)
N(3)-C(2)-C(9)	122.9(3)	C(1)-C(2)-C(9)	129.6(3)
C(2)-N(3)-C(4)	111.1(2)	C(2)-N(3)-C(15)	128.1(2)
C(4)-N(3)-C(15)	120.1(2)	O(16)-C(4)-N(3)	121.6(3)
O(16)-C(4)-C(5)	134.0(3)	N(3)-C(4)-C(5)	104.3(2)
C(6)-C(5)-C(1)	110.4(2)	C(6)-C(5)-C(4)	142.3(3)
C(1)-C(5)-C(4)	107.3(3)	C(5)-C(6)-C(7)	106.4(2)
C(5)-C(6)-C(17)	128.1(3)	C(7)-C(6)-C(17)	125.5(3)
C(8)-C(7)-C(25)	127.4(3)	C(8)-C(7)-C(6)	108.7(3)
C(25)-C(7)-C(6)	123.7(3)	O(27)-C(8)-C(7)	131.2(3)
O(27)-C(8)-C(1)	121.8(3)	C(7)-C(8)-C(1)	107.0(2)
C(10)-C(9)-C(14)	119.9(3)	C(10)-C(9)-C(2)	118.9(3)
C(14)-C(9)-C(2)	121.1(3)	C(11)-C(10)-C(9)	119.2(3)
C(12)-C(11)-C(10)	121.0(3)	C(11)-C(12)-C(13)	120.2(3)
C(12)-C(13)-C(14)	120.0(3)	C(13)-C(14)-C(9)	119.7(3)
C(22)-C(17)-C(18)	117.7(3)	C(22)-C(17)-C(6)	121.9(3)
C(18)-C(17)-C(6)	120.3(3)	C(19)-C(18)-C(17)	121.2(3)
C(20)-C(19)-C(18)	119.6(3)	C(19)-C(20)-O(23)	115.9(3)
C(19)-C(20)-C(21)	120.7(3)	O(23)-C(20)-C(21)	123.4(3)
C(20)-C(21)-C(22)	119.1(3)	C(17)-C(22)-C(21)	121.6(3)
C(20)-O(23)-C(24)	117.2(2)	N(26)-C(25)-C(7)	178.1(4)
C(8)-O(27)-C(28)	119.8(2)		

Appendix 6

X-ray structure analysis



A. Crystal Data

Empirical Formula	C H N O Cl
Formula Weight	346.77
Crystal Color, Habit	red, plate
Crystal Dimensions/mm	0.40 × 0.25 × 0.05
Crystal System	triclinic
Lattice Type	Primitive
a/Å	10.03(2)
b/Å	11.75(2)
c/Å	7.01(1)
α ( )	91.5(1)
β ( )	101.7(2)
γ ( )	90.0(1)
V/Å	809(2)
Space Group	*P*-1(#2)
Z	2
F_{000}	356.00
D_{calc}/gcm^{-}	1.423
$\mu(MoK\alpha)/cm^{-1}$	2.52

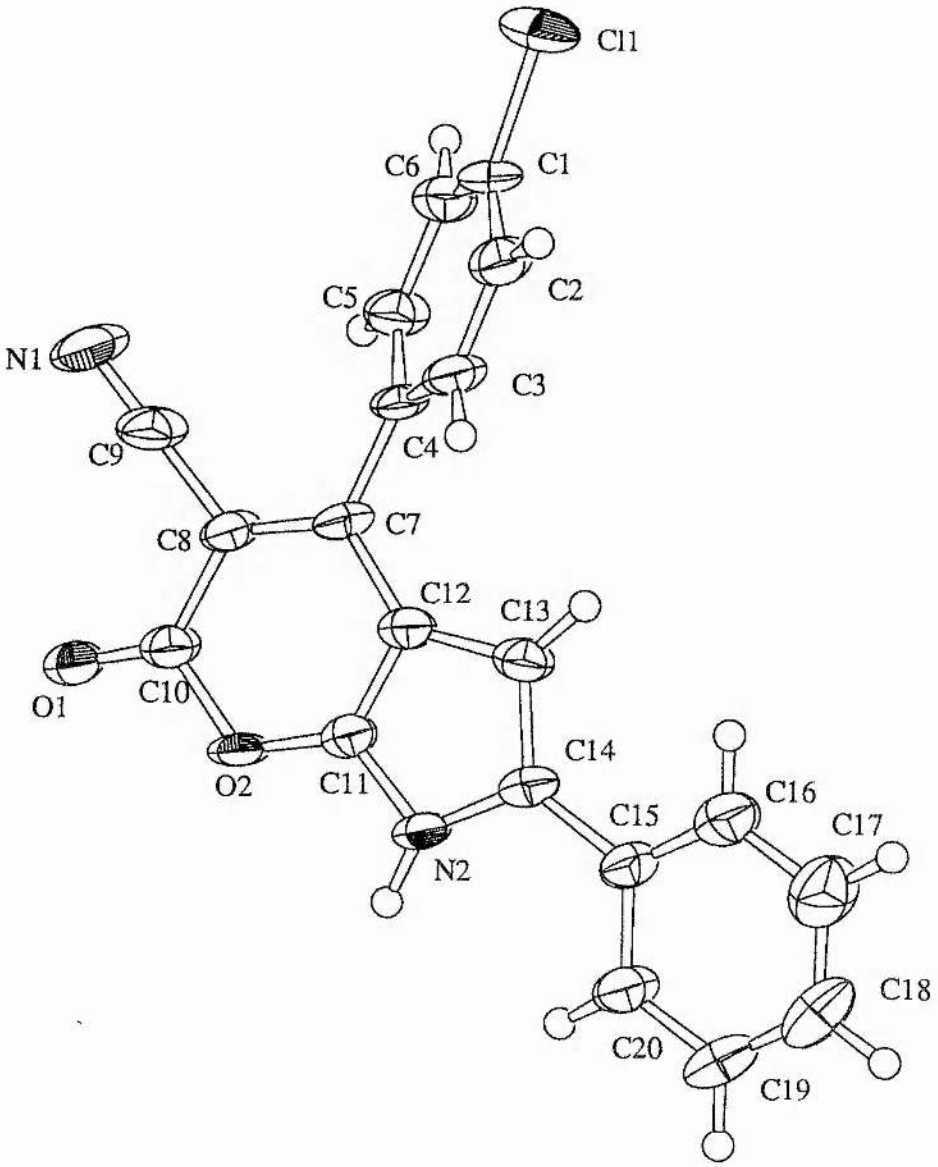
B. Data Acquisition

Max. 2θ ( ) for reflections	45.1
Reflections measured	2097
Reflections with $I > 3\sigma(I)$	1249

C. Structure solution and refinement

Solution method	Direct Methods (SIR92)
No. of variables in LS	231
R, Rw	0.059, 0.072
Density max in final ΔF-map (eÅ)	0.27

Dr. P. Lightfoot
University of St. Andrews



Structure diagram and atom numbering scheme

Positional parameters and B(eq)

atom	x	y	z	B(eq)
Cl(1)	-0.0031(2)	0.7127(1)	0.8155(3)	5.62(6)
O(1)	0.5022(5)	0.2008(3)	0.2856(7)	4.1(1)
O(2)	0.4297(5)	0.1026(3)	0.5109(6)	3.5(1)
N(1)	0.3561(7)	0.4752(5)	0.2538(10)	5.4(2)
N(2)	0.3563(6)	0.0097(4)	0.7660(8)	3.4(1)
C(1)	0.0867(8)	0.5888(5)	0.7719(10)	3.7(2)
C(2)	0.0197(7)	0.4852(6)	0.7575(10)	3.8(2)
C(3)	0.0895(7)	0.3906(5)	0.7126(10)	3.5(2)
C(4)	0.2208(7)	0.3981(5)	0.6824(9)	2.9(2)
C(5)	0.2866(7)	0.5046(5)	0.7085(10)	3.6(2)
C(6)	0.2170(8)	0.6002(5)	0.7563(10)	3.9(2)
C(7)	0.2932(7)	0.2974(5)	0.6224(10)	3.3(2)
C(8)	0.3587(7)	0.3001(5)	0.4724(10)	3.2(2)
C(9)	0.3580(7)	0.3987(6)	0.351(1)	3.9(2)
C(10)	0.4381(7)	0.2037(5)	0.410(1)	3.3(2)
C(11)	0.3626(7)	0.1025(5)	0.6555(10)	3.2(2)
C(12)	0.2932(7)	0.1919(5)	0.7209(9)	3.3(2)
C(13)	0.2418(7)	0.1516(5)	0.8831(10)	3.5(2)
C(14)	0.2846(7)	0.0384(5)	0.9071(10)	3.6(2)
C(15)	0.2580(7)	-0.0416(5)	1.0535(10)	3.3(2)
C(16)	0.1685(8)	-0.0173(6)	1.171(1)	4.7(2)
C(17)	0.1437(9)	-0.0914(7)	1.310(1)	5.6(2)
C(18)	0.2129(9)	-0.1945(7)	1.329(1)	5.2(2)
C(19)	0.3009(8)	-0.2223(5)	1.212(1)	4.7(2)
C(20)	0.3276(7)	-0.1468(5)	1.0749(10)	3.8(2)
H(1)	-0.0708	0.4792	0.7777	4.5278
H(2)	0.0459	0.3183	0.7018	4.1167
H(3)	0.3782	0.5112	0.6933	4.3632
H(4)	0.2611	0.6723	0.7773	4.6344
H(5)	0.1892	0.1932	0.9595	4.3313
H(6)	0.1219	0.0531	1.1565	5.6309
H(7)	0.0467	-0.0719	1.3969	6.6726
H(8)	0.1974	-0.2460	1.4255	6.1807
H(9)	0.3445	-0.2940	1.2246	5.6591
H(10)	0.3917	-0.1657	0.9966	4.5802
H(11)	0.410(8)	-0.047(6)	0.734(1)	6(1)

Intramolecular Distances (Å)

atom	atom	distance	atom	atom	distance
Cl(1)	C(1)	1.765(6)	C(7)	C(8)	1.349(8)
O(1)	C(10)	1.181(7)	C(7)	C(12)	1.434(8)
O(2)	C(10)	1.410(7)	C(8)	C(9)	1.455(9)
O(2)	C(11)	1.325(7)	C(8)	C(10)	1.492(9)
N(1)	C(9)	1.139(8)	C(11)	C(12)	1.380(9)
N(2)	C(11)	1.363(8)	C(12)	C(13)	1.431(8)
N(2)	C(14)	1.371(8)	C(13)	C(14)	1.402(8)
C(1)	C(2)	1.383(9)	C(14)	C(15)	1.472(8)
C(1)	C(6)	1.341(9)	C(15)	C(16)	1.363(9)
C(2)	C(3)	1.377(9)	C(15)	C(20)	1.416(9)
C(3)	C(4)	1.379(9)	C(16)	C(17)	1.38(1)
C(4)	C(5)	1.406(8)	C(17)	C(18)	1.39(1)
C(4)	C(7)	1.484(8)	C(18)	C(19)	1.36(1)
C(5)	C(6)	1.392(9)	C(19)	C(20)	1.391(9)

Intramolecular Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(10)	O(2)	C(11)	119.5(5)	O(1)	C(10)	C(8)	128.8(6)
C(11)	N(2)	C(14)	108.4(5)	O(2)	C(10)	C(8)	113.9(6)
Cl(1)	C(1)	C(2)	118.4(6)	O(2)	C(11)	N(2)	122.7(5)
Cl(1)	C(1)	C(6)	118.1(5)	O(2)	C(11)	C(12)	127.3(6)
C(2)	C(1)	C(6)	123.5(6)	N(2)	C(11)	C(12)	109.9(6)
C(1)	C(2)	C(3)	117.3(7)	C(7)	C(12)	C(11)	116.9(6)
C(2)	C(3)	C(4)	121.7(6)	C(7)	C(12)	C(13)	136.5(6)
C(3)	C(4)	C(5)	118.6(6)	C(11)	C(12)	C(13)	106.6(5)
C(3)	C(4)	C(7)	121.8(6)	C(12)	C(13)	C(14)	106.2(5)
C(5)	C(4)	C(7)	119.6(6)	N(2)	C(14)	C(13)	108.8(6)
C(4)	C(5)	C(6)	119.8(6)	N(2)	C(14)	C(15)	123.3(5)
C(1)	C(6)	C(5)	118.8(6)	C(13)	C(14)	C(15)	127.9(6)
C(4)	C(7)	C(8)	122.0(5)	C(14)	C(15)	C(16)	122.0(6)
C(4)	C(7)	C(12)	120.6(6)	C(14)	C(15)	C(20)	119.6(6)
C(8)	C(7)	C(12)	117.4(6)	C(16)	C(15)	C(20)	118.5(6)
C(7)	C(8)	C(9)	123.1(6)	C(15)	C(16)	C(17)	122.4(7)
C(7)	C(8)	C(10)	124.8(5)	C(16)	C(17)	C(18)	118.4(7)
C(9)	C(8)	C(10)	112.2(6)	C(17)	C(18)	C(19)	120.8(7)
N(1)	C(9)	C(8)	179.0(8)	C(18)	C(19)	C(20)	120.8(7)
O(1)	C(10)	O(2)	117.2(5)	C(15)	C(20)	C(19)	119.2(7)

Torsion or Conformation Angles (°)

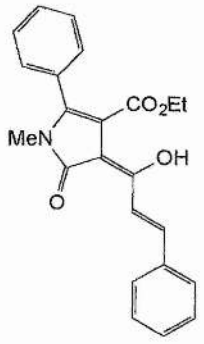
(1)	(2)	(3)	(4)	angle
Cl(1)	C(1)	C(2)	C(3)	176.4(5)
Cl(1)	C(1)	C(6)	C(5)	-175.6(5)
O(1)	C(10)	O(2)	C(11)	177.9(6)
O(1)	C(10)	C(8)	C(7)	-176.8(7)
O(1)	C(10)	C(8)	C(9)	4(1)
O(2)	C(10)	C(8)	C(7)	5(1)
O(2)	C(10)	C(8)	C(9)	-173.9(6)
O(2)	C(11)	N(2)	C(14)	177.6(6)
O(2)	C(11)	C(12)	C(7)	0(1)
O(2)	C(11)	C(12)	C(13)	-178.1(7)
N(1)	C(9)	C(8)	C(7)	-101(40)
N(1)	C(9)	C(8)	C(10)	79(40)
N(2)	C(11)	O(2)	C(10)	-176.6(6)
N(2)	C(11)	C(12)	C(7)	178.5(6)
N(2)	C(11)	C(12)	C(13)	0.5(8)
N(2)	C(14)	C(13)	C(12)	-1.0(8)
N(2)	C(14)	C(15)	C(16)	-169.1(7)
N(2)	C(14)	C(15)	C(20)	11(1)
C(1)	C(2)	C(3)	C(4)	0(1)
C(1)	C(6)	C(5)	C(4)	-2(1)
C(2)	C(1)	C(6)	C(5)	5(1)
C(2)	C(3)	C(4)	C(5)	3(1)
C(2)	C(3)	C(4)	C(7)	-176.3(6)
C(3)	C(2)	C(1)	C(6)	-4(1)
C(3)	C(4)	C(5)	C(6)	-2(1)
C(3)	C(4)	C(7)	C(8)	131.2(7)
C(3)	C(4)	C(7)	C(12)	-48(1)
C(4)	C(7)	C(8)	C(9)	-3(1)
C(4)	C(7)	C(8)	C(10)	177.4(7)
C(4)	C(7)	C(12)	C(11)	179.8(6)
C(4)	C(7)	C(12)	C(13)	-3(1)
C(5)	C(4)	C(7)	C(8)	-48(1)
C(5)	C(4)	C(7)	C(12)	132.9(7)
C(6)	C(5)	C(4)	C(7)	177.1(6)
C(7)	C(12)	C(13)	C(14)	-177.1(8)
C(8)	C(7)	C(12)	C(11)	1(1)
C(8)	C(7)	C(12)	C(13)	178.3(8)
C(8)	C(10)	O(2)	C(11)	-4.1(9)
C(9)	C(8)	C(7)	C(12)	175.3(7)
C(10)	O(2)	C(11)	C(12)	2(1)
C(10)	C(8)	C(7)	C(12)	-4(1)
C(11)	N(2)	C(14)	C(13)	1.3(8)
C(11)	N(2)	C(14)	C(15)	-179.9(6)
C(11)	C(12)	C(13)	C(14)	0.3(8)
C(12)	C(11)	N(2)	C(14)	-1.1(8)
C(12)	C(13)	C(14)	C(15)	-179.8(7)
C(13)	C(14)	C(15)	C(16)	10(1)
C(13)	C(14)	C(15)	C(20)	-170.0(7)
C(14)	C(15)	C(16)	C(17)	-179.4(7)
C(14)	C(15)	C(20)	C(19)	-179.4(7)
C(15)	C(16)	C(17)	C(18)	3(1)
C(15)	C(20)	C(19)	C(18)	-3(1)

Torsion or Conformation Angles (°) (continued)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
C(16)	C(15)	C(20)	C(19)	1(1)					
C(16)	C(17)	C(18)	C(19)	-1(1)					
C(17)	C(16)	C(15)	C(20)	0(1)					
C(17)	C(18)	C(19)	C(20)	2(1)					

Appendix 7

X-ray structure analysis



A. Crystal Data

Empirical Formula	C H NO
Formula Weight	375.41
Crystal Color, Habit	-
Crystal Dimensions/mm	-
Crystal System	monoclinic
Lattice Type	Primitive
a/Å	10.492(2)
b/Å	35.420(6)
c/Å	10.385(2)
α (°)	90
β (°)	90.26(2)
γ (°)	90
V/Å	3859.3(12)
Space Group	*P*2 /*c* (#14)
Z	8
F000	792
Dcalc/gcm	1.292
μ(MoKα)/cm	0.89

B. Data Acquisition

Max. 2θ (°) for reflections	50.0
Reflections measured	6481
Reflections with $I > 2\sigma(I)$	3086

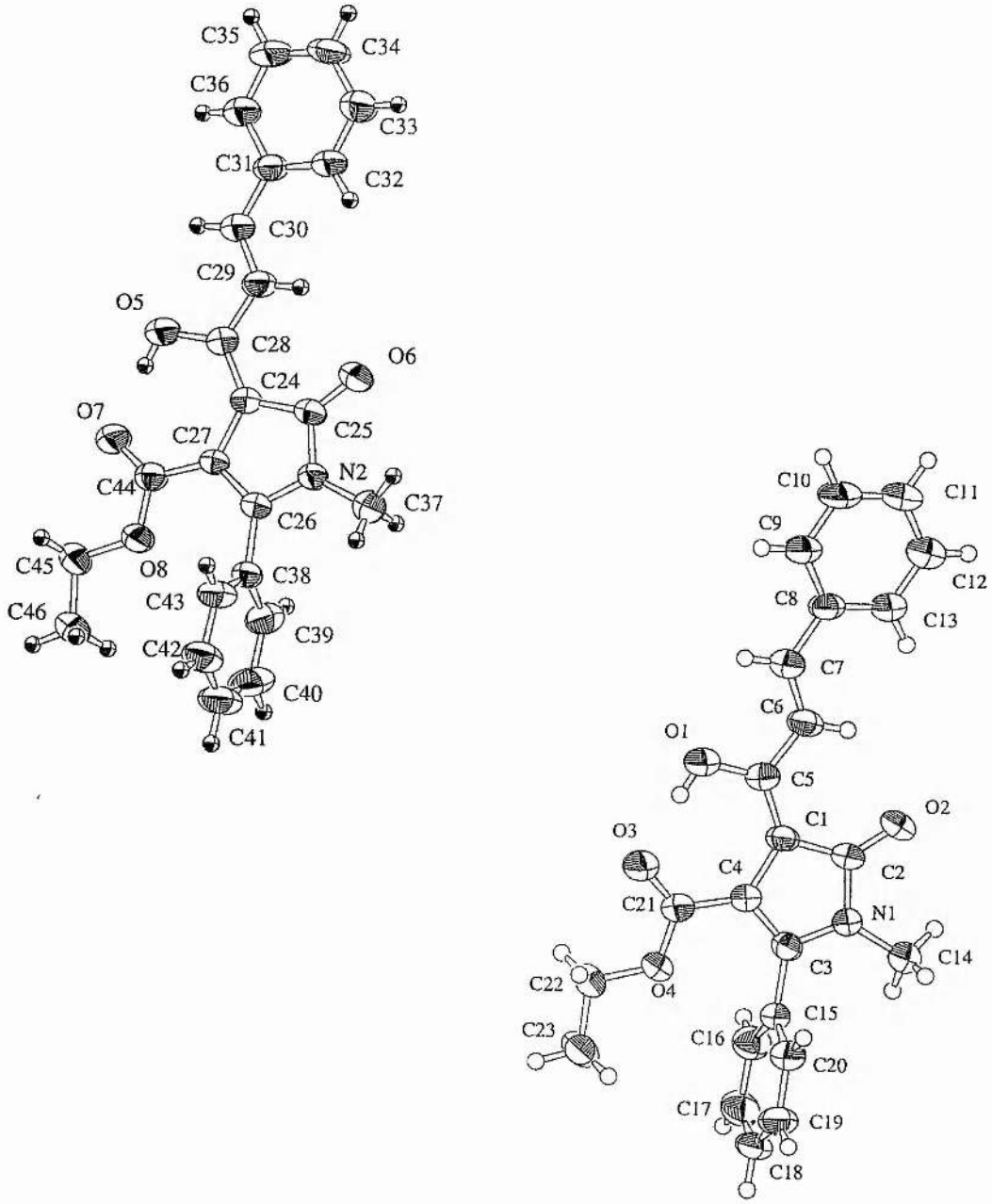
C. Structure solution and refinement

Solution method	SHELXS-86
No. of variables in LS	509
R	0.057
Density max in final ΔF-map (eÅ)	0.210

ORTEP diagram & numbering scheme:

The structure refined with two independent molecules in the asymmetric unit which are chemically identical. An ORTEP diagram for each of these molecules is shown on the next page.

Dr.P Lightfoot
University of St. Andrews



Structure diagram and atom numbering scheme

Positional parameters and U_{eq}

atom	x	y	z	U
O1	0.1487(3)	0.31357(6)	0.0776(3)	0.0690(8)
H1	0.1673(30)	0.29242(14)	0.0517(33)	0.103
O2	-0.1576(2)	0.29615(7)	0.3591(3)	0.0692(8)
O3	0.1907(2)	0.24781(7)	-0.0025(3)	0.0678(8)
O4	0.1438(2)	0.18950(6)	0.0577(2)	0.0574(7)
O5	-0.3252(3)	-0.06297(6)	0.5953(3)	0.0641(8)
H5	-0.3085(28)	-0.0419(2)	0.5676(30)	0.096
O6	-0.6328(2)	-0.04609(7)	0.8756(3)	0.0648(8)
O7	-0.2836(2)	0.00303(7)	0.5157(2)	0.0651(8)
O8	-0.3402(2)	0.06124(6)	0.5695(2)	0.0560(7)
N1	-0.1148(3)	0.23413(7)	0.3121(3)	0.0499(8)
N2	-0.5844(3)	0.01603(7)	0.8365(3)	0.0481(8)
C1	0.0054(3)	0.27668(9)	0.2022(4)	0.0465(9)
C2	-0.0957(3)	0.27280(9)	0.2971(4)	0.0511(10)
C3	-0.0354(3)	0.21396(10)	0.2322(3)	0.0443(9)
C4	0.0389(3)	0.23807(9)	0.1634(3)	0.0437(9)
C5	0.0549(3)	0.31097(9)	0.1629(4)	0.0486(9)
C6	0.0117(3)	0.34674(9)	0.2122(4)	0.0528(9)
H6	-0.0502(3)	0.34669(9)	0.2761(4)	0.063
C7	0.0557(3)	0.37985(9)	0.1713(4)	0.0544(10)
H7	0.1165(3)	0.37907(9)	0.1065(4)	0.065
C8	0.0187(4)	0.41741(10)	0.2172(4)	0.0520(9)
C9	0.0632(4)	0.44925(10)	0.1544(4)	0.0635(11)
H9	0.1176(4)	0.44652(10)	0.0845(4)	0.076
C10	0.0278(4)	0.48510(11)	0.1938(5)	0.0838(15)
H10	0.0586(4)	0.50617(11)	0.1505(5)	0.101
C11	-0.0523(4)	0.48962(11)	0.2966(5)	0.0829(15)
H11	-0.0782(4)	0.51359(11)	0.3219(5)	0.099
C12	-0.0938(4)	0.45809(12)	0.3619(5)	0.0855(15)
H12	-0.1448(4)	0.46090(12)	0.4343(5)	0.103
C13	-0.0603(4)	0.42248(11)	0.3211(4)	0.0696(12)
H13	-0.0917(4)	0.40150(11)	0.3645(4)	0.083
C14	-0.2063(4)	0.21890(10)	0.4025(4)	0.0645(11)
H14A	-0.2851(8)	0.2138(6)	0.3585(6)	0.097
H14B	-0.2209(18)	0.2369(3)	0.4700(13)	0.097
H14C	-0.1736(11)	0.1959(4)	0.4389(18)	0.097
C15	-0.0439(3)	0.17189(10)	0.2276(3)	0.0434(9)
C16	0.0373(4)	0.14912(11)	0.2977(4)	0.0596(11)
H16	0.0981(4)	0.15985(11)	0.3519(4)	0.071
C17	0.0281(4)	0.11011(12)	0.2873(4)	0.0703(13)
H17	0.0846(4)	0.09477(12)	0.3325(4)	0.084
C18	-0.0629(4)	0.09431(11)	0.2115(4)	0.0663(12)
H18	-0.0693(4)	0.06817(11)	0.2062(4)	0.080
C19	-0.1453(4)	0.11644(10)	0.1429(4)	0.0628(11)
H19	-0.2082(4)	0.10543(10)	0.0920(4)	0.075
C20	-0.1347(3)	0.15539(10)	0.1495(4)	0.0544(10)
H20	-0.1891(3)	0.17049(10)	0.1009(4)	0.065
C21	0.1295(3)	0.22620(10)	0.0662(4)	0.0474(9)
C22	0.2357(3)	0.17480(10)	-0.0326(4)	0.0547(10)
H22A	0.3194(3)	0.18534(10)	-0.0959(4)	0.066
H22B	0.2109(3)	0.14094(10)	-0.1203(4)	0.066
C23	0.2366(4)	0.13282(10)	-0.0130(5)	0.0688(12)
H23A	0.2965(4)	0.12148(10)	-0.0710(4)	0.103
H23B	0.1530(4)	0.12288(10)	-0.0296(4)	0.103
H23C	0.2610(4)	0.12725(10)	0.0742(4)	0.103
C24	-0.4696(3)	-0.02621(9)	0.7186(4)	0.0426(8)
C25	-0.5692(3)	-0.00263(9)	0.8161(3)	0.0469(9)
C26	-0.5946(3)	0.03644(10)	0.7578(3)	0.0425(9)

Positional parameters and U_{eq} (continued)

atom	x	y	z	U
C27	-0.4344(3)	0.01232(9)	0.6832(3)	0.0413(9)
C28	-0.4189(3)	-0.06047(9)	0.6810(4)	0.0478(9)
C29	-0.4608(3)	-0.09649(9)	0.7315(4)	0.0506(9)
H29	-0.5217(3)	-0.09655(9)	0.7963(4)	0.061
C30	-0.4164(3)	-0.12960(9)	0.6898(4)	0.0532(10)
H30	-0.3584(3)	-0.12884(9)	0.6224(4)	0.064
C31	-0.4494(3)	-0.16683(9)	0.7393(4)	0.0490(9)
C32	-0.5309(4)	-0.17202(10)	0.8413(4)	0.0592(11)
H32	-0.5695(4)	-0.15104(10)	0.8783(4)	0.071
C33	-0.5572(4)	-0.20732(11)	0.8903(4)	0.0684(12)
H33	-0.6124(4)	-0.20997(11)	0.9595(4)	0.082
C34	-0.5013(4)	-0.23854(10)	0.8362(4)	0.0730(13)
H34	-0.5179(4)	-0.26245(10)	0.8691(4)	0.088
C35	-0.4210(4)	-0.23434(11)	0.7337(5)	0.0798(14)
H35	-0.3834(4)	-0.25545(11)	0.6966(5)	0.096
C36	-0.3955(4)	-0.19876(10)	0.6853(4)	0.0675(12)
H36	-0.3413(4)	-0.19625(10)	0.6152(4)	0.081
C37	-0.6738(4)	0.03106(10)	0.9307(4)	0.0634(11)
H37A	-0.6886(19)	0.0125(3)	0.9964(14)	0.095
H37B	-0.7529(9)	0.0371(7)	0.8887(6)	0.095
H37C	-0.6387(11)	0.0534(4)	0.9691(18)	0.095
C38	-0.5007(3)	0.07840(10)	0.7653(3)	0.0433(9)
C39	-0.5811(4)	0.10068(11)	0.6932(4)	0.0605(11)
H39	-0.6443(4)	0.08965(11)	0.6427(4)	0.073
C40	-0.5678(5)	0.13956(12)	0.6958(4)	0.0743(13)
H40	-0.6223(5)	0.15463(12)	0.6472(4)	0.089
C41	-0.4751(5)	0.15580(13)	0.7694(4)	0.0723(14)
H41	-0.4662(5)	0.18192(13)	0.7702(4)	0.087
C42	-0.3954(4)	0.13401(11)	0.8418(4)	0.0646(11)
H42	-0.3316(4)	0.14523(11)	0.8911(4)	0.077
C43	-0.4094(4)	0.09539(10)	0.8420(4)	0.0573(10)
H43	-0.3571(4)	0.08064(10)	0.8942(4)	0.069
C44	-0.3458(3)	0.02402(10)	0.5839(4)	0.0474(9)
C45	-0.2542(3)	0.07656(9)	0.4739(4)	0.0546(10)
H45A	-0.2803(3)	0.06889(9)	0.3881(4)	0.066
H45B	-0.1679(3)	0.06779(9)	0.4893(4)	0.066
C46	-0.2615(4)	0.11864(10)	0.4875(4)	0.0645(11)
H46A	-0.2060(4)	0.13028(10)	0.4259(4)	0.097
H46B	-0.2357(4)	0.12574(10)	0.5729(4)	0.097
H46C	-0.3474(4)	0.12683(10)	0.4723(4)	0.097

Intramolecular distances (Å)

atom	atom	distance	atom	atom	distance
O1	C5	1.330(4)	C16	C17	1.389(5)
O2	C2	1.235(4)	C17	C18	1.355(6)
O3	C21	1.230(4)	C18	C19	1.365(5)
O4	C21	1.312(4)	C19	C20	1.386(5)
O4	C22	1.445(4)	C22	C23	1.501(5)
O5	C28	1.332(4)	C24	C28	1.382(4)
O6	C25	1.233(4)	C24	C27	1.461(4)
O7	C44	1.219(4)	C24	C25	1.464(5)
O8	C44	1.328(4)	C26	C27	1.370(4)
O8	C45	1.450(4)	C26	C38	1.489(5)
N1	C3	1.378(4)	C27	C44	1.452(5)
N1	C2	1.393(4)	C28	C29	1.448(5)
N1	C14	1.450(4)	C29	C30	1.335(4)
N2	C26	1.378(4)	C30	C31	1.458(5)
N2	C25	1.395(4)	C31	C32	1.376(5)
N2	C37	1.459(4)	C31	C36	1.384(5)
C1	C5	1.383(4)	C32	C33	1.378(5)
C1	C2	1.441(5)	C33	C34	1.373(5)
C6	C7	1.331(5)	C34	C35	1.369(6)
C7	C8	1.466(5)	C35	C36	1.383(5)
C8	C13	1.375(5)	C38	C39	1.374(5)
C8	C9	1.385(5)	C38	C43	1.382(5)
C9	C10	1.385(5)	C39	C40	1.385(5)
C10	C11	1.371(6)	C40	C41	1.361(6)
C11	C12	1.378(6)	C41	C42	1.362(6)
C12	C13	1.377(5)	C42	C43	1.376(5)
C15	C16	1.379(5)	C45	C46	1.499(5)
C15	C20	1.378(5)			

Non-bonded contacts (Å)

atom	atom	distance
O1	O3	2.51
O3	H1	1.70
O5	O7	2.52
O7	H5	1.70

Bond Angles (°)

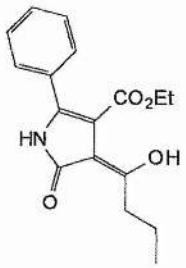
atom	atom	atom	angle
C21	O4	C22	118.5(3)
C44	O8	C45	118.5(3)
C3	N1	C2	110.8(3)
C3	N1	C14	126.9(3)
C2	N1	C14	122.3(3)
C26	N2	C25	110.8(3)
C26	N2	C37	126.9(3)
C25	N2	C37	122.3(3)
C5	C1	C2	123.9(3)
C5	C1	C4	130.2(3)
C2	C1	C4	105.9(3)
O2	C2	N1	121.6(3)
O2	C2	C1	132.5(3)
N1	C2	C1	105.9(3)
C4	C3	N1	109.9(3)
C4	C3	C15	130.1(3)
N1	C3	C15	120.0(3)
C3	C4	C21	124.2(3)
C3	C4	C1	107.5(3)
C21	C4	C1	128.3(3)
O1	C5	C1	122.5(3)
O1	C5	C6	114.3(3)
C1	C5	C6	123.2(3)
C7	C6	C5	123.4(4)
C6	C7	C8	127.1(4)
C13	C8	C9	118.0(3)
C13	C8	C7	122.3(3)
C9	C8	C7	119.7(4)
C8	C9	C10	121.1(4)
C11	C10	C9	120.2(4)
C10	C11	C12	119.0(4)
C13	C12	C11	120.6(4)
C8	C13	C12	121.1(4)
C16	C15	C20	119.1(4)
C16	C15	C3	122.0(3)
C20	C15	C3	118.9(3)
C15	C16	C17	119.9(4)
C18	C17	C16	120.3(4)
C17	C18	C19	120.6(4)
C18	C19	C20	119.7(4)
C15	C20	C19	120.4(4)
O3	C21	O4	121.2(3)
O3	C21	C4	124.7(3)
O4	C21	C4	114.2(3)
O4	C22	C23	105.8(3)
C28	C24	C27	130.7(3)
C28	C24	C25	123.2(3)
C27	C24	C25	106.0(3)
O6	C25	N2	121.5(3)
O6	C25	C24	132.7(3)
N2	C25	C24	105.8(3)
C27	C26	N2	109.8(3)
C27	C26	C38	129.6(3)
N2	C26	C38	120.6(3)
C26	C27	C44	124.8(3)
C26	C27	C24	107.6(3)
C44	C27	C24	127.5(3)
O5	C28	C24	122.2(3)
O5	C28	C29	114.2(3)
C24	C28	C29	123.7(3)
C30	C29	C28	123.4(4)
C29	C30	C31	126.6(4)
C32	C31	C36	117.3(3)
C32	C31	C30	122.8(3)
C36	C31	C30	119.9(4)
C31	C32	C33	122.1(3)
C34	C33	C32	119.6(4)
C35	C34	C33	119.7(4)
C34	C35	C36	120.2(4)
C35	C36	C31	121.1(4)
C39	C38	C43	119.1(4)
C39	C38	C26	121.9(3)
C43	C38	C26	118.9(3)
C38	C39	C40	119.9(4)
C41	C40	C39	120.2(4)
C40	C41	C42	120.4(4)
C41	C42	C43	119.9(4)
C42	C43	C38	120.4(4)
O7	C44	O8	121.1(3)
O7	C44	C27	125.4(3)
O8	C44	C27	113.1(3)
O8	C45	C46	106.3(3)

Torsion Angles (°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C3	N1	C2	O2	179.6(3)	C26	N2	C25	O6	-179.0(3)
C14	N1	C2	O2	-1.1(6)	C37	N2	C25	O6	1.4(5)
C3	N1	C2	C1	-1.2(4)	C26	N2	C25	C24	1.3(4)
C14	N1	C2	C1	178.1(3)	C37	N2	C25	C24	-178.3(3)
C5	C1	C2	O2	0.9(7)	C28	C24	C25	O6	-5.8(6)
C4	C1	C2	O2	-179.6(4)	C27	C24	C25	O6	178.4(4)
C5	C1	C2	N1	-178.2(3)	C28	C24	C25	N2	173.8(3)
C4	C1	C2	N1	1.3(4)	C27	C24	C25	N2	-2.0(4)
C2	N1	C3	C4	0.6(4)	C25	N2	C26	C27	0.0(4)
C14	N1	C3	C4	-178.7(3)	C37	N2	C26	C27	179.5(3)
C2	N1	C3	C15	-177.1(3)	C25	N2	C26	C38	-178.0(3)
C14	N1	C3	C15	3.6(5)	C37	N2	C26	C38	1.6(5)
N1	C3	C4	C21	-177.3(3)	N2	C26	C27	C44	176.3(3)
C15	C3	C4	C21	0.1(6)	C38	C26	C27	C44	-6.0(6)
N1	C3	C4	C1	0.3(4)	N2	C26	C27	C24	-1.3(4)
C15	C3	C4	C1	177.6(3)	C38	C26	C27	C24	176.4(3)
C5	C1	C4	C3	178.5(4)	C28	C24	C27	C26	-173.4(4)
C2	C1	C4	C3	-1.0(4)	C25	C24	C27	C26	2.0(4)
C5	C1	C4	C21	-4.0(6)	C28	C24	C27	C44	9.1(6)
C2	C1	C4	C21	176.5(3)	C25	C24	C27	C44	-175.5(3)
C2	C1	C5	O1	178.8(3)	C27	C24	C28	O5	-2.9(6)
C4	C1	C5	O1	-0.6(6)	C25	C24	C28	O5	-177.6(3)
C2	C1	C5	C6	0.2(6)	C27	C24	C28	C29	176.3(3)
C4	C1	C5	C6	-179.3(3)	C25	C24	C28	C29	1.5(6)
O1	C5	C6	C7	3.8(5)	O5	C28	C29	C30	-4.6(5)
C1	C5	C6	C7	-177.4(4)	C24	C28	C29	C30	176.3(4)
C5	C6	C7	C8	-179.0(3)	C28	C29	C30	C31	177.2(3)
C6	C7	C8	C13	6.7(6)	C29	C30	C31	C32	-2.0(6)
C6	C7	C8	C9	-172.8(4)	C29	C30	C31	C36	179.7(4)
C13	C8	C9	C10	-0.8(6)	C36	C31	C32	C33	1.1(6)
C7	C8	C9	C10	178.7(4)	C30	C31	C32	C33	-177.3(4)
C8	C9	C10	C11	0.0(7)	C31	C32	C33	C34	-0.3(6)
C9	C10	C11	C12	1.9(8)	C32	C33	C34	C35	-0.5(7)
C10	C11	C12	C13	-3.0(7)	C33	C34	C35	C36	0.4(7)
C9	C8	C13	C12	-0.3(6)	C34	C35	C36	C31	0.5(7)
C7	C8	C13	C12	-179.8(4)	C32	C31	C36	C35	-1.2(6)
C11	C12	C13	C8	2.3(7)	C30	C31	C36	C35	177.3(4)
C4	C3	C15	C16	85.5(5)	C27	C26	C38	C39	93.9(5)
N1	C3	C15	C16	-97.4(4)	N2	C26	C38	C39	-88.6(4)
C4	C3	C15	C20	-93.6(5)	C27	C26	C38	C43	-82.8(5)
N1	C3	C15	C20	83.6(4)	N2	C26	C38	C43	94.7(4)
C20	C15	C16	C17	1.0(5)	C43	C38	C39	C40	1.6(5)
C3	C15	C16	C17	-178.1(3)	C26	C38	C39	C40	-175.1(3)
C15	C16	C17	C18	-2.0(6)	C38	C39	C40	C41	0.1(6)
C16	C17	C18	C19	1.1(6)	C39	C40	C41	C42	-0.5(6)
C17	C18	C19	C20	0.9(6)	C40	C41	C42	C43	-0.8(6)
C16	C15	C20	C19	0.9(5)	C41	C42	C43	C38	2.5(6)
C3	C15	C20	C19	-180.0(3)	C39	C38	C43	C42	-2.9(5)
C18	C19	C20	C15	-1.9(6)	C26	C38	C43	C42	173.9(3)
C22	O4	C21	O3	1.3(5)	C45	O8	C44	O7	-2.5(5)
C22	O4	C21	C4	-177.5(3)	C45	O8	C44	C27	179.5(4)
C3	C4	C21	O3	174.9(3)	C26	C27	C44	O7	-179.1(4)
C1	C4	C21	O3	-2.2(6)	C24	C27	C44	O7	-2.0(6)
C3	C4	C21	O4	-6.3(5)	C26	C27	C44	O8	-1.2(5)
C1	C4	C21	O4	176.7(3)	C24	C27	C44	O8	176.0(3)
C21	O4	C22	C23	176.9(3)	C44	O8	C45	C46	-175.7(3)

Appendix 8

X-ray structure analysis



A. Crystal Data

Empirical Formula	$C_{15}H_{19}NO_3$
Formula Weight	301.34
Crystal Color, Habit	green, block
Crystal Dimensions/mm	0.50 × 0.30 × 0.30
Crystal System	triclinic
Lattice Type	Primitive
a/Å	9.314(3)
b/Å	11.121(4)
c/Å	7.883(3)
α (°)	95.07(3)
β (°)	102.39(3)
γ (°)	96.04(3)
V/Å^3	787.9(5)
Space Group	*P*-1(#2)
Z	2
F_{000}	320.00
D_{calc}/gcm^{-3}	1.270
μ(MoKα)/cm^{-1}	0.90

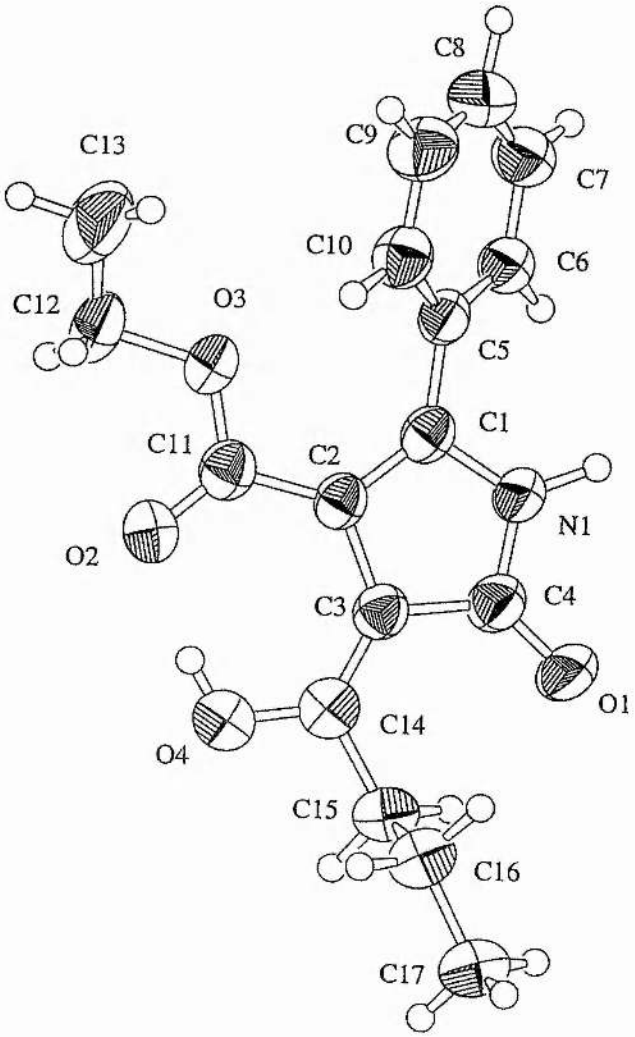
B. Data Acquisition

Max. 2θ (°) for reflections	50.0
Reflections measured	2955
Reflections with $I > 3\sigma(I)$	1702

C. Structure solution and refinement

Solution method	Direct Methods (SIR92)
No. of variables in LS	248
R, Rw	0.045, 0.042
Density max in final Δ*F*-map (eÅ^{-3})	0.16

Dr. J. Wightman
University of St. Andrews



Structure diagram with atom numbering scheme

Positional parameters and B(eq)

atom	x	y	z	B(eq)
O(1)	0.4590(3)	-0.1365(2)	0.6068(3)	6.56(6)
O(2)	0.7892(3)	-0.0344(2)	1.2784(3)	6.17(6)
O(3)	0.8904(2)	0.1373(2)	1.2066(3)	5.68(6)
O(4)	0.5999(3)	-0.2149(2)	1.1411(3)	5.89(6)
N(1)	0.6324(3)	0.0328(2)	0.7035(3)	4.71(6)
C(1)	0.7337(3)	0.0820(3)	0.8550(4)	3.95(7)
C(2)	0.7248(3)	0.0085(3)	0.9836(4)	3.89(6)
C(3)	0.6109(3)	-0.0960(3)	0.9070(4)	4.09(7)
C(4)	0.5549(3)	-0.0755(3)	0.7264(4)	4.83(8)
C(5)	0.8243(3)	0.1971(3)	0.8438(4)	3.94(7)
C(6)	0.7566(3)	0.2901(3)	0.7659(4)	4.53(7)
C(7)	0.8398(4)	0.3978(3)	0.7504(5)	5.50(9)
C(8)	0.9920(4)	0.4124(3)	0.8083(5)	6.06(10)
C(9)	1.0595(4)	0.3199(4)	0.8816(5)	6.05(10)
C(10)	0.9784(3)	0.2128(3)	0.9013(4)	4.90(8)
C(11)	0.8018(3)	0.0327(3)	1.1663(4)	4.39(7)
C(12)	0.9727(5)	0.1675(5)	1.3885(5)	7.7(1)
C(13)	1.0994(6)	0.2504(5)	1.3941(6)	12.4(2)
C(14)	0.5559(3)	-0.1945(3)	0.9765(4)	4.49(8)
C(15)	0.4423(3)	-0.2951(3)	0.8736(5)	4.97(8)
C(16)	0.5132(4)	-0.3934(3)	0.7882(5)	5.51(9)
C(17)	0.3986(5)	-0.4982(4)	0.6916(6)	6.7(1)
H(1)	0.650(4)	0.276(3)	0.715(4)	8.1623
H(2)	1.021(4)	0.148(3)	0.964(4)	8.1623
H(3)	1.163(4)	0.332(3)	0.929(4)	8.1623
H(4)	1.050(4)	0.492(3)	0.791(4)	8.1623
H(5)	0.794(4)	0.458(3)	0.691(4)	8.1623
H(6)	0.606(3)	0.071(3)	0.584(4)	8.1623
H(7)	0.669(4)	-0.155(3)	1.197(5)	8.1623
H(8)	0.388(4)	-0.335(3)	0.959(4)	8.1623
H(9)	0.371(4)	-0.264(3)	0.778(4)	8.1623
H(10)	0.559(4)	-0.355(3)	0.696(4)	8.1623
H(11)	0.581(4)	-0.428(3)	0.880(4)	8.1623
H(12)	0.440(4)	-0.561(3)	0.629(5)	8.1623
H(13)	0.323(4)	-0.464(3)	0.608(5)	8.1623
H(14)	0.355(4)	-0.540(3)	0.778(4)	8.162
H(17)	0.916(4)	0.160(3)	1.468(5)	8.1623
H(18)	1.054(4)	0.100(3)	1.404(4)	8.1623
H(19)	1.1676	0.2511	1.5027	14.9128
H(20)	1.1435	0.2265	1.3012	14.9128
H(21)	1.0709	0.3295	1.3831	14.9128

Intramolecular Distances (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(4)	1.243(3)	C(8)	C(9)	1.369(5)
O(2)	C(11)	1.222(3)	C(9)	C(10)	1.381(5)
O(3)	C(11)	1.325(3)	C(14)	C(15)	1.500(4)
O(3)	C(12)	1.465(4)	C(15)	C(16)	1.516(5)
O(4)	C(14)	1.322(3)	C(16)	C(17)	1.519(5)
C(12)	C(13)	1.409(6)			
N(1)	C(1)	1.382(3)			
N(1)	C(4)	1.384(4)			
C(1)	C(2)	1.368(4)			
C(1)	C(5)	1.478(4)			
C(2)	C(3)	1.477(4)			
C(2)	C(11)	1.452(4)			
C(3)	C(4)	1.455(4)			
C(3)	C(14)	1.368(4)			
C(5)	C(6)	1.388(4)			
C(5)	C(10)	1.397(4)			
C(6)	C(7)	1.385(4)			
C(7)	C(8)	1.380(5)			

Non-bonded contacts (Å)

atom	atom	distance
O2	O4	2.52
O2	H7	1.64

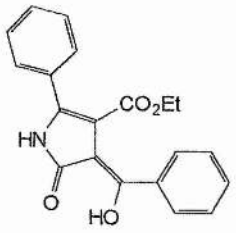
Intramolecular Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(11)	O(3)	C(12)	117.5(3)	C(6)	C(5)	C(10)	118.7(3)
C(1)	N(1)	C(4)	111.3(2)	C(5)	C(6)	C(7)	120.7(3)
N(1)	C(1)	C(2)	109.3(3)	C(6)	C(7)	C(8)	120.2(3)
N(1)	C(1)	C(5)	115.7(2)	C(7)	C(8)	C(9)	119.4(3)
C(2)	C(1)	C(5)	135.0(3)	C(8)	C(9)	C(10)	121.4(3)
C(1)	C(2)	C(3)	107.4(2)	C(5)	C(10)	C(9)	119.7(3)
C(1)	C(2)	C(11)	126.9(3)	O(2)	C(11)	O(3)	120.5(3)
C(3)	C(2)	C(11)	125.4(3)	O(2)	C(11)	C(2)	125.1(3)
C(2)	C(3)	C(4)	105.8(2)	O(3)	C(11)	C(2)	114.4(3)
C(2)	C(3)	C(14)	132.2(3)	O(3)	C(12)	C(13)	109.1(3)
C(4)	C(3)	C(14)	122.0(3)	O(4)	C(14)	C(3)	124.2(3)
O(1)	C(4)	N(1)	122.6(3)	O(4)	C(14)	C(15)	111.6(3)
O(1)	C(4)	C(3)	131.3(3)	C(3)	C(14)	C(15)	124.2(3)
N(1)	C(4)	C(3)	106.1(2)	C(14)	C(15)	C(16)	111.8(3)
C(1)	C(5)	C(6)	119.7(2)	C(15)	C(16)	C(17)	111.7(3)
C(1)	C(5)	C(10)	121.6(3)				

Torsion or Conformation Angles (°)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
O(1)	C(4)	N(1)	C(1)	-179.2(3)	C(1)	C(5)	C(10)	C(9)	177.2(3)
O(1)	C(4)	C(3)	C(2)	179.8(3)	C(2)	C(1)	N(1)	C(4)	-0.9(3)
O(1)	C(4)	C(3)	C(14)	-2.0(6)	C(2)	C(1)	C(5)	C(6)	-133.7(4)
O(2)	C(11)	O(3)	C(12)	0.7(5)	C(2)	C(1)	C(5)	C(10)	49.8(5)
O(2)	C(11)	C(2)	C(1)	178.7(3)	C(2)	C(3)	C(14)	C(15)	-177.6(3)
O(2)	C(11)	C(2)	C(3)	4.9(5)	C(2)	C(11)	O(3)	C(12)	-179.6(3)
O(3)	C(11)	C(2)	C(1)	-1.0(4)	C(3)	C(2)	C(1)	C(5)	-178.9(3)
O(3)	C(11)	C(2)	C(3)	-174.8(3)	C(3)	C(14)	C(15)	C(16)	86.8(4)
O(4)	C(14)	C(3)	C(2)	0.0(5)	C(4)	N(1)	C(1)	C(5)	179.0(3)
O(4)	C(14)	C(3)	C(4)	-177.8(3)	C(4)	C(3)	C(2)	C(11)	174.2(3)
O(4)	C(14)	C(15)	C(16)	-91.0(3)	C(4)	C(3)	C(14)	C(15)	4.7(5)
N(1)	C(1)	C(2)	C(3)	0.9(3)	C(5)	C(1)	C(2)	C(11)	6.4(5)
N(1)	C(1)	C(2)	C(11)	-173.8(3)	C(5)	C(6)	C(7)	C(8)	1.8(5)
N(1)	C(1)	C(5)	C(6)	46.4(4)	C(5)	C(10)	C(9)	C(8)	0.7(6)
N(1)	C(1)	C(5)	C(10)	-130.0(3)	C(6)	C(5)	C(10)	C(9)	0.7(5)
N(1)	C(4)	C(3)	C(2)	0.1(3)	C(6)	C(7)	C(8)	C(9)	-0.3(6)
N(1)	C(4)	C(3)	C(14)	178.4(3)	C(7)	C(6)	C(5)	C(10)	-2.0(5)
C(1)	N(1)	C(4)	C(3)	0.4(3)	C(7)	C(8)	C(9)	C(10)	-0.9(6)
C(1)	C(2)	C(3)	C(4)	-0.6(3)	C(11)	O(3)	C(12)	C(13)	156.5(4)
C(1)	C(2)	C(3)	C(14)	-178.7(3)	C(11)	C(2)	C(3)	C(14)	-3.8(5)
C(1)	C(5)	C(6)	C(7)	-178.6(3)	C(14)	C(15)	C(16)	C(17)	177.2(3)

Appendix 9 X-ray structure analysis



A. Crystal Data

Empirical Formula	C H NO
Formula Weight	335.36
Crystal Color, Habit	orange, block
Crystal Dimensions/mm	0.35 × 0.20 × 0.15
Crystal System	triclinic
Lattice Type	Primitive
a/Å	10.374(3)
b/Å	12.908(7)
c/Å	6.945(4)
α (°)	97.58(4)
β ( )	93.25(3)
γ (°)	69.45(3)
V/Å³	863.1(7)
Space Group	*P*-1(#2)
Z	2
F_{000}	352.00
D_{calc}/gcm^{-}	1.290
μ(MoKα)/cm^{-1}	0.90

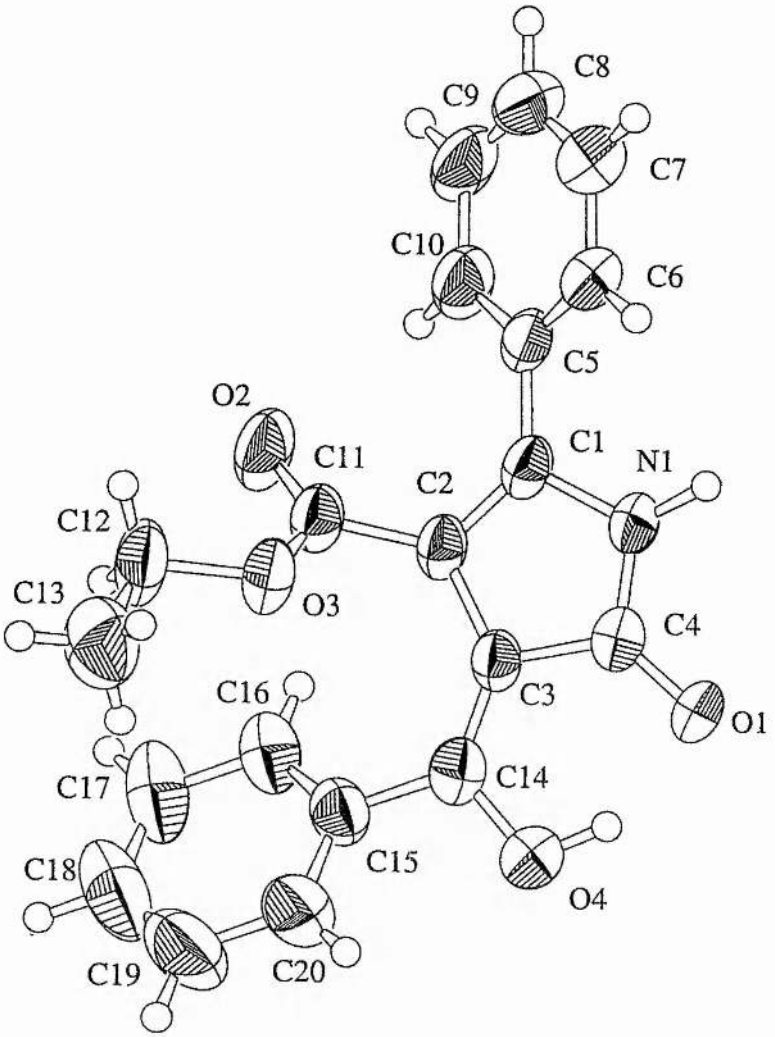
B. Data Acquisition

Max. 2θ ( ) for reflections	50.0
Reflections measured	3223
Reflections with $I > 3\sigma(I)$	1702

C. Structure solution and refinement

Solution method	Direct Methods (SIR92)
No. of variables in LS	233
R, Rw	0.044, 0.033
Density max in final Δ*F*-map (eÅ)	0.34

Dr. P. Lightfoot
University of St. Andrews



Structure diagram and atom numbering scheme

Positional parameters and B(eq)

atom	x	y	z	B(eq)
O(1)	0.6408(2)	-0.0445(2)	0.1863(3)	4.70(6)
O(2)	0.3372(3)	0.3591(2)	0.7140(4)	6.53(7)
O(3)	0.5463(2)	0.3394(2)	0.6107(3)	4.88(6)
O(4)	0.8026(2)	-0.0241(2)	0.4714(4)	5.79(7)
N(1)	0.4275(3)	0.0969(2)	0.2117(3)	3.94(7)
C(1)	0.3649(3)	0.1946(2)	0.3398(4)	3.86(8)
C(2)	0.4553(3)	0.2038(2)	0.4844(4)	3.83(8)
C(3)	0.5809(3)	0.1068(2)	0.4512(4)	3.72(8)
C(4)	0.5580(4)	0.0438(3)	0.2726(4)	4.00(9)
C(5)	0.2257(3)	0.2677(2)	0.2896(5)	4.06(9)
C(6)	0.1926(4)	0.2911(3)	0.1010(5)	4.92(10)
C(7)	0.0621(4)	0.3596(3)	0.0532(6)	6.7(1)
C(8)	-0.0359(4)	0.4033(3)	0.1932(7)	7.4(1)
C(9)	-0.0051(4)	0.3802(3)	0.3803(7)	7.2(1)
C(10)	0.1251(4)	0.3119(3)	0.4316(5)	5.7(1)
C(11)	0.4369(4)	0.3070(3)	0.6167(5)	4.44(9)
C(12)	0.5452(4)	0.4348(3)	0.7493(5)	6.5(1)
C(13)	0.6796(5)	0.4498(3)	0.7377(6)	8.2(1)
C(14)	0.7026(4)	0.0669(3)	0.5513(5)	4.41(9)
C(15)	0.7406(4)	0.1106(3)	0.7441(5)	4.76(10)
C(16)	0.6425(4)	0.1600(3)	0.8863(5)	5.4(1)
C(17)	0.6792(5)	0.2014(3)	1.0676(6)	7.1(1)
C(18)	0.8139(7)	0.1927(4)	1.1061(7)	8.9(2)
C(19)	0.9118(5)	0.1431(4)	0.9663(8)	8.9(2)
C(20)	0.8762(4)	0.1015(3)	0.7847(6)	6.9(1)
H(1)	0.2603	0.2597	0.0029	5.8945
H(2)	0.0407	0.3762	-0.0766	8.0768
H(3)	-0.1258	0.4498	0.1604	8.8836
H(4)	-0.0739	0.4116	0.4768	8.5985
H(5)	0.1453	0.2954	0.5616	6.8377
H(6)	0.4729	0.4997	0.7175	7.7774
H(7)	0.5323	0.4214	0.8768	7.7774
H(8)	0.6924	0.4622	0.6094	9.8746
H(9)	0.7515	0.3847	0.7701	9.8746
H(10)	0.6813	0.5121	0.8262	9.8746
H(11)	0.5496	0.1657	0.8598	6.4877
H(12)	0.6114	0.2356	1.1649	8.5636
H(13)	0.8391	0.2213	1.2299	10.6351
H(14)	1.0047	0.1370	0.9939	10.6615
H(15)	0.9445	0.0669	0.6885	8.2072
H(16)	0.395(3)	0.081(3)	0.078(5)	8.1174
H(17)	0.768(4)	-0.053(3)	0.355(5)	8.1174

Intramolecular Distances (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(4)	1.260(3)	C(9)	C(10)	1.386(5)
O(2)	C(11)	1.204(4)	C(12)	C(13)	1.482(5)
O(3)	C(11)	1.345(4)	C(14)	C(15)	1.471(4)
O(3)	C(12)	1.456(3)	C(15)	C(16)	1.382(5)
O(4)	C(14)	1.342(4)	C(15)	C(20)	1.385(5)
N(1)	C(1)	1.414(3)	C(16)	C(17)	1.388(5)
N(1)	C(4)	1.357(4)	C(17)	C(18)	1.376(6)
C(1)	C(2)	1.357(4)	C(18)	C(19)	1.369(7)
C(1)	C(5)	1.473(4)	C(19)	C(20)	1.386(6)
C(2)	C(3)	1.460(4)			
C(2)	C(11)	1.475(4)			
C(3)	C(4)	1.447(4)			
C(3)	C(14)	1.372(4)			
C(5)	C(6)	1.380(4)			
C(5)	C(10)	1.392(4)			
C(6)	C(7)	1.383(5)			
C(7)	C(8)	1.364(5)			
C(8)	C(9)	1.367(6)			

Non-bonded contacts (Å)

atom	atom	distance
O1	O4	2.57
O1	H17	1.70

Intramolecular Bond Angles (°)

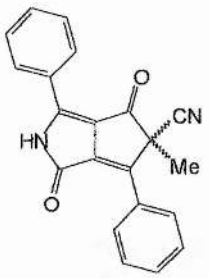
atom	atom	atom	angle	atom	atom	atom	angle
C(11)	O(3)	C(12)	115.5(3)	C(7)	C(8)	C(9)	120.2(4)
C(1)	N(1)	C(4)	110.0(2)	C(8)	C(9)	C(10)	121.0(4)
N(1)	C(1)	C(2)	109.2(3)	C(5)	C(10)	C(9)	118.9(4)
N(1)	C(1)	C(5)	117.8(3)	O(2)	C(11)	O(3)	123.1(3)
C(2)	C(1)	C(5)	132.9(3)	O(2)	C(11)	C(2)	126.1(3)
C(1)	C(2)	C(3)	107.4(2)	O(3)	C(11)	C(2)	110.7(3)
C(1)	C(2)	C(11)	123.4(3)	O(3)	C(12)	C(13)	107.8(3)
C(3)	C(2)	C(11)	127.6(3)	O(4)	C(14)	C(3)	118.9(3)
C(2)	C(3)	C(4)	106.1(3)	O(4)	C(14)	C(15)	113.0(3)
C(2)	C(3)	C(14)	134.5(3)	C(3)	C(14)	C(15)	128.1(3)
C(4)	C(3)	C(14)	119.4(3)	C(14)	C(15)	C(16)	120.7(3)
O(1)	C(4)	N(1)	124.9(3)	C(14)	C(15)	C(20)	119.9(4)
O(1)	C(4)	C(3)	127.8(3)	C(16)	C(15)	C(20)	119.5(3)
N(1)	C(4)	C(3)	107.3(3)	C(15)	C(16)	C(17)	120.3(4)
C(1)	C(5)	C(6)	120.6(3)	C(16)	C(17)	C(18)	119.8(4)
C(1)	C(5)	C(10)	120.1(3)	C(17)	C(18)	C(19)	120.2(4)
C(6)	C(5)	C(10)	119.3(3)	C(18)	C(19)	C(20)	120.4(5)
C(5)	C(6)	C(7)	120.7(3)	C(15)	C(20)	C(19)	119.8(4)
C(6)	C(7)	C(8)	119.7(4)				

Torsion or Conformation Angles (°)

(1)	(2)	(3)	(4)	angle
O(1)	C(4)	N(1)	C(1)	-178.5(3)
O(1)	C(4)	C(3)	C(2)	177.8(3)
O(1)	C(4)	C(3)	C(14)	-3.9(5)
O(2)	C(11)	C(3)	C(12)	7.6(5)
O(2)	C(11)	C(2)	C(1)	54.4(5)
O(2)	C(11)	C(2)	C(3)	-141.7(4)
O(3)	C(11)	C(2)	C(1)	-123.4(3)
O(3)	C(11)	C(2)	C(3)	40.5(5)
O(4)	C(14)	C(3)	C(2)	-176.0(3)
O(4)	C(14)	C(3)	C(4)	6.3(5)
O(4)	C(14)	C(15)	C(16)	-146.3(3)
O(4)	C(14)	C(15)	C(20)	33.1(5)
N(1)	C(1)	C(2)	C(3)	-1.2(4)
N(1)	C(1)	C(2)	C(11)	165.5(3)
N(1)	C(1)	C(5)	C(6)	-42.7(4)
N(1)	C(1)	C(5)	C(10)	135.8(3)
N(1)	C(4)	C(3)	C(2)	-2.6(3)
N(1)	C(4)	C(3)	C(14)	175.6(3)
C(1)	N(1)	C(4)	C(3)	1.9(3)
C(1)	C(2)	C(3)	C(4)	2.3(4)
C(1)	C(2)	C(3)	C(14)	-175.5(4)
C(1)	C(5)	C(6)	C(7)	180.0(3)
C(1)	C(5)	C(10)	C(9)	-179.9(3)
C(2)	C(1)	N(1)	C(4)	-0.5(4)
C(2)	C(1)	C(5)	C(6)	132.5(4)
C(2)	C(1)	C(5)	C(10)	-49.0(5)

(1)	(2)	(3)	(4)	angle
C(2)	C(3)	C(14)	C(15)	4.9(6)
C(2)	C(11)	O(3)	C(12)	-174.5(3)
C(3)	C(2)	C(1)	C(5)	-176.7(3)
C(3)	C(14)	C(15)	C(16)	32.8(5)
C(3)	C(14)	C(15)	C(20)	-147.8(4)
C(4)	N(1)	C(1)	C(5)	175.8(3)
C(4)	C(3)	C(2)	C(11)	-163.7(3)
C(4)	C(3)	C(14)	C(15)	-172.7(3)
C(5)	C(1)	C(2)	C(11)	-10.0(6)
C(5)	C(6)	C(7)	C(8)	-1.0(6)
C(5)	C(10)	C(9)	C(8)	0.9(6)
C(6)	C(5)	C(10)	C(9)	-1.4(5)
C(6)	C(7)	C(8)	C(9)	0.5(7)
C(7)	C(6)	C(5)	C(10)	1.5(5)
C(7)	C(8)	C(9)	C(10)	-0.5(7)
C(11)	O(3)	C(12)	C(13)	173.4(3)
C(11)	C(2)	C(3)	C(14)	18.5(6)
C(14)	C(15)	C(16)	C(17)	-179.8(3)
C(14)	C(15)	C(20)	C(19)	179.8(4)
C(15)	C(16)	C(17)	C(18)	-0.3(6)
C(15)	C(20)	C(19)	C(18)	0.2(6)
C(16)	C(15)	C(20)	C(19)	-0.8(6)
C(16)	C(17)	C(18)	C(19)	-0.3(8)
C(17)	C(16)	C(15)	C(20)	0.8(6)
C(17)	C(18)	C(19)	C(20)	1.3(8)

Appendix 10 X-ray structure analysis



"Many crystals were twinned and it took several attempts until one was found amenable for data collection. This turned out to be a dimethylated derivative (compound **90**) and it is unambiguous that nitrogen (N1) is methylated. The structure refined to a chiral space group with disorder.

There is disorder at carbon C(5), with the CH, and CN functionalities being 'above' the plane of the central heterocycle 65 % of the time, and 'below' this plane 35 % of the time, with the CN in the converse positions. This is allowed for in the refinement by giving both carbons [C(21) and C22)] full occupancy and N(21A) and N(21B) occupancies of 65 % and 35 % respectively. The phenyl groups were refiined as rigid bodies"

A. Crystal Data

Empirical Formula	C H N O
Formula Weight	340.37
Crystal Color, Habit	orange, plate
Crystal Dimensions/mm	0.1 x 0.06 x 0.01
Crystal System	monoclinic
Lattice Type	Primitive
a/Å	10.656(2)
b/Å	7.5930(14)
c/Å	10.942(2)
α ( )	90.0
β ( )	96.517(4)
γ ( )	90.0
V/Å	879.7(3)
Space Group	*P*2(1) (#4)
Z	2
F_{000}	356
D_{calc}/gcm^{-}	1.285
μ(MoKα)/cm^{-1}	0.083

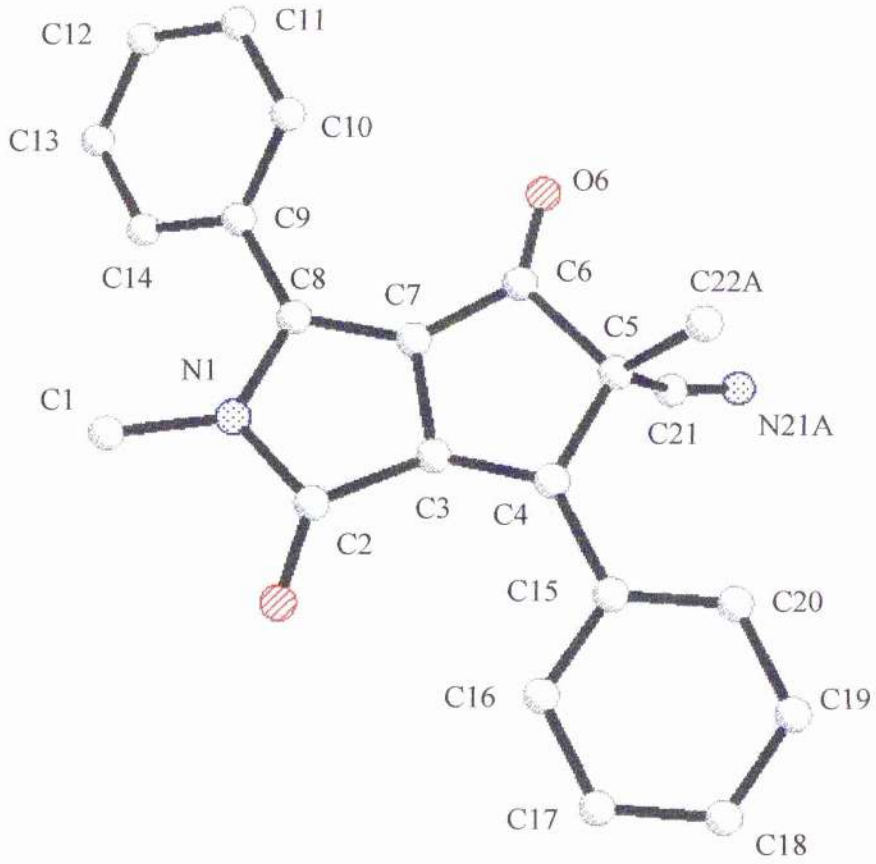
B. Data Acquisition

Max. 2θ ( ) for reflections	-
Reflections measured	2382
Reflections with $I > 2\sigma(I)$	781

C. Structure solution and refinement

Solution method	SHELXS-97
R	0.1193
Density max in final ΔF-map (eÅ)	0.403

Dr. A Slawin
University of St. Andrews



Structure diagram with atom numbering scheme

Positional parameters and U_{ani}

atom	x	y	z	U_{ani}
C1	0.8466(3)	0.4107(9)	0.7296(3)	0.0821(15)
H1A	0.7607	0.4248	0.6938	0.123
H1B	0.8779	0.2986	0.7061	0.123
H1C	0.8975	0.5030	0.7010	0.123
N1	0.8521(2)	0.4193(6)	0.8617(2)	0.0646(10)
C2	0.9684(3)	0.4007(7)	0.9369(3)	0.0514(11)
O2	1.0712(2)	0.3983(5)	0.89553(19)	0.0738(9)
C3	0.9357(3)	0.4191(6)	1.0668(2)	0.0425(10)
C4	0.9909(3)	0.4029(6)	1.1855(2)	0.0491(10)
C5	0.8841(3)	0.3954(6)	1.2645(3)	0.0602(12)
C6	0.7572(3)	0.4143(7)	1.1746(3)	0.0581(11)
O6	0.6549(2)	0.4165(7)	1.20967(18)	0.0987(11)
C7	0.7992(3)	0.4207(7)	1.0567(2)	0.0522(11)
C8	0.7511(4)	0.4131(7)	0.9326(3)	0.0748(13)
C9	0.61572(18)	0.4385(3)	0.88079(17)	0.0715(14)
C10	0.5240(2)	0.3578(4)	0.9422(2)	0.108(2)
H10A	0.5473	0.2957	1.0145	0.129
C11	0.39739(19)	0.3698(5)	0.8955(3)	0.134(2)
H11A	0.3360	0.3157	0.9365	0.160
C12	0.36257(19)	0.4625(6)	0.7874(3)	0.0884(19)
H12A	0.2779	0.4705	0.7562	0.106
C13	0.4543(3)	0.5433(5)	0.7261(3)	0.109(2)
H13A	0.4310	0.6053	0.6538	0.130
C14	0.5809(2)	0.5313(4)	0.7727(2)	0.095(2)
H14A	0.6423	0.5853	0.7317	0.114
C15	1.12534(15)	0.4144(5)	1.23431(14)	0.0774(13)
C16	1.21589(18)	0.4396(7)	1.15402(17)	0.129(2)
H16A	1.1918	0.4457	1.0697	0.155
C17	1.34249(18)	0.4559(9)	1.1997(3)	0.244(5)
H17A	1.4031	0.4728	1.1460	0.293
C18	1.37855(17)	0.4468(10)	1.3257(3)	0.225(4)
H18A	1.4633	0.4577	1.3562	0.270
C19	1.2880(2)	0.4216(9)	1.40596(19)	0.1132(19)
H19A	1.3121	0.4155	1.4902	0.136
C20	1.16140(19)	0.4053(7)	1.36028(15)	0.0803(14)
H20A	1.1008	0.3884	1.4140	0.096
C21	0.8791(4)	0.5638(7)	1.3385(4)	0.0921(18)
N21A	0.8735(7)	0.6471(9)	1.4235(6)	0.126(3)
C22A	0.8847(4)	0.2314(8)	1.3446(4)	0.111(2)
H22A	0.9619	0.2271	1.3991	0.167
H22B	0.8786	0.1285	1.2932	0.167
H22C	0.8142	0.2351	1.3918	0.167
C22B	0.8847(4)	0.2314(8)	1.3446(4)	0.111(2)
N21B	0.8687(7)	0.1620(10)	1.4070(6)	0.033(2)

Intramolecular Distances (Å)

atom	atom	distance
C1	N1	1.442(4)
N1	C8	1.397(4)
N1	C2	1.414(4)
C2	O2	1.232(4)
C2	C3	1.508(4)
C3	C4	1.369(4)
C3	C7	1.447(4)
C4	C15	1.474(3)
C4	C5	1.506(5)
C5	C21	1.518(7)
C5	C22B	1.523(7)
C5	C22A	1.523(7)
C5	C6	1.586(4)
C6	O6	1.196(4)
C6	C7	1.414(4)
C7	C8	1.397(4)
C8	C9	1.501(4)
C9	C10	1.3900
C9	C14	1.3900
C10	C11	1.3900
C11	C12	1.3900
C12	C13	1.3900
C13	C14	1.3900
C15	C16	1.3900
C15	C20	1.3900
C16	C17	1.3900
C17	C18	1.3900
C18	C19	1.3900
C19	C20	1.3900
C21	N21A	1.132(8)
C22B	N21B	0.894(9)

Intramolecular Bond Angles (°)

atom	atom	atom	angle
C8	N1	C2	110.7(2)
C8	N1	C1	127.5(3)
C2	N1	C1	120.8(3)
O2	C2	N1	123.0(3)
O2	C2	C3	131.1(3)
N1	C2	C3	104.9(2)
C4	C3	C7	113.1(3)
C4	C3	C2	140.0(3)
C7	C3	C2	105.5(2)
C3	C4	C15	129.3(3)
C3	C4	C5	106.1(3)
C15	C4	C5	124.1(2)
C4	C5	C21	110.4(4)
C4	C5	C22A	114.0(4)
C21	C5	C22A	112.3(3)
C4	C5	C6	106.7(2)
C21	C5	C6	100.1(3)
C22B	C5	C6	112.2(3)
C22A	C5	C6	112.2(3)
O6	C6	C7	133.4(3)
O6	C6	C5	123.1(3)
C7	C6	C5	103.5(3)
C8	C7	C6	140.0(3)
C8	C7	C3	109.2(3)
C6	C7	C3	110.5(2)
N1	C8	C7	108.5(3)
N1	C8	C9	123.6(2)
C7	C8	C9	126.3(3)
C10	C9	C14	120.0
C10	C9	C8	117.34(19)
C14	C9	C8	122.59(18)
C9	C10	C11	120.0
C12	C11	C10	120.0
C13	C12	C11	120.0
C14	C13	C12	120.0
C13	C14	C9	120.0
C16	C15	C20	120.0
C16	C15	C4	119.66(14)
C20	C15	C4	120.31(14)
C15	C16	C17	120.0
C18	C17	C16	120.0
C17	C18	C19	120.0
C18	C19	C20	120.0
C19	C20	C15	120.0
N21A	C21	C5	156.6(6)
N21B	C22B	C5	158.9(8)

Torsion or Conformation Angles (°)

(1)	(2)	(3)	(4)	angle
C8	N1	C2	O2	178.5(5)
C1	N1	C2	O2	9.2(8)
C8	N1	C2	C3	-11.4(5)
C1	N1	C2	C3	179.4(5)
O2	C2	C3	C4	-18.0(10)
N1	C2	C3	C4	172.9(6)
O2	C2	C3	C7	177.4(5)
N1	C2	C3	C7	8.4(5)
C7	C3	C4	C15	-173.0(4)
C2	C3	C4	C15	23.2(9)
C7	C3	C4	C5	-0.9(5)
C2	C3	C4	C5	-164.6(5)
C3	C4	C5	C21	-109.3(4)
C15	C4	C5	C21	63.4(5)
C3	C4	C5	C22A	123.1(4)
C15	C4	C5	C22A	-64.2(6)
C3	C4	C5	C6	-1.4(5)
C15	C4	C5	C6	171.3(4)
C4	C5	C6	O6	-178.6(5)
C21	C5	C6	O6	-63.5(6)
C22A	C5	C6	O6	55.8(7)
C4	C5	C6	C7	3.0(5)
C21	C5	C6	C7	118.1(4)
C22A	C5	C6	C7	-122.5(4)
O6	C6	C7	C8	-9.0(12)
C5	C6	C7	C8	169.1(7)
O6	C6	C7	C3	178.3(6)
C5	C6	C7	C3	-3.6(5)
C4	C3	C7	C8	-172.0(4)
C2	C3	C7	C8	-2.7(5)
C4	C3	C7	C6	3.1(6)
C2	C3	C7	C6	172.3(4)
C2	N1	C8	C7	10.1(6)
C1	N1	C8	C7	178.4(5)
C2	N1	C8	C9	176.7(4)
C1	N1	C8	C9	-15.0(8)
C6	C7	C8	N1	-176.9(6)
C3	C7	C8	N1	-4.2(6)
C6	C7	C8	C9	16.9(10)
C3	C7	C8	C9	-170.4(4)
N1	C8	C9	C10	152.7(4)
C7	C8	C9	C10	-43.1(6)
N1	C8	C9	C14	-24.2(6)
C7	C8	C9	C14	140.0(4)
C14	C9	C10	C11	0.0
C8	C9	C10	C11	-177.0(2)
C9	C10	C11	C12	0.0
C10	C11	C12	C13	0.0
C11	C12	C13	C14	0.0
C12	C13	C14	C9	0.0
C10	C9	C14	C13	0.0
C8	C9	C14	C13	176.9(3)
C3	C4	C15	C16	-2.2(6)
C5	C4	C15	C16	-173.1(4)

Torsion or Conformation Angles (°) (continued)

(1)	(2)	(3)	(4)	angle
C3	C4	C15	C20	175.8(4)
C5	C4	C15	C20	4.9(6)
C20	C15	C16	C17	0.0
C4	C15	C16	C17	178.1(3)
C15	C16	C17	C18	0.0
C16	C17	C18	C19	0.0
C17	C18	C19	C20	0.0
C18	C19	C20	C15	0.0
C16	C15	C20	C19	0.0
C4	C15	C20	C19	-178.0(3)
C4	C5	C21	N21A	-130.9(13)
C22A	C5	C21	N21A	-2.4(14)
C6	C5	C21	N21A	116.9(13)
C4	C5	C22B	N21B	157.0(18)
C21	C5	C22B	N21B	30.4(19)
C6	C5	C22B	N21B	-81.5(19)

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"Sometimes, the more you think, the more there is no real answer"

Anonymous